Textbooks in Contemporary Dentistry

Marco A. Peres
Jose Leopoldo Ferreira Antunes
Richard G. Watt *Editors*

Oral Epidemiology

A Textbook on Oral Health Conditions, Research Topics and Methods

Springer

Textbooks in Contemporary Dentistry

This textbook series presents the most recent advances in all fields of dentistry, with the aim of bridging the gap between basic science and clinical practice. It will equip readers with an excellent knowledge of how to provide optimal care reflecting current understanding and utilizing the latest materials and techniques. Each volume is written by internationally respected experts in the field who ensure that information is conveyed in a concise, consistent, and readily intelligible manner with the aid of a wealth of informative illustrations. *Textbooks in Contemporary Dentistry* will be especially valuable for advanced students, practitioners in the early stages of their career, and university instructors.

More information about this series at http://www.springer.com/series/14362

Marco A. Peres • Jose Leopoldo Ferreira Antunes
Richard G. Watt
Editors

Oral Epidemiology

A Textbook on Oral Health Conditions, Research Topics and Methods

Springer

Editors
Marco A. Peres
National Dental Research Institute,
National Dental Centre Singapore
Singapore

ACP Oral Health, Health Services and
Systems Research Programme, Duke-NUS
Medical School
Singapore, Singapore

Richard G. Watt
Dept. of Epidemiology and Public Health
University College London
London, United Kingdom

Jose Leopoldo Ferreira Antunes
School of Public Health
University of São Paulo Faculty
of Public Health
São Paulo, São Paulo, Brazil

Originally published by Livraria Santos Editora Ltda., São Paulo, 2013

ISSN 2524-4612 ISSN 2524-4620 (electronic)
Textbooks in Contemporary Dentistry
ISBN 978-3-030-50122-8 ISBN 978-3-030-50123-5 (eBook)
https://doi.org/10.1007/978-3-030-50123-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The book edited by Professors Peres, Antunes, and Watt, with dozens of collaborators from 12 countries, represents a landmark publication in the field of Oral Health Epidemiology. Having been involved in Epidemiology for over four decades, I witnessed its evolution from a relatively narrow discipline aimed at studying communicable diseases to a broad endeavor that covers all types of conditions related to health and illness. In addition to disease-specific research, Epidemiology earned several qualifiers to describe its growing scope: social, genetic, environmental, life-course, and behavioral are a few descriptors that have been and continue to be applied to our discipline. This book is a stellar example of how such a multitude of approaches can be brought together in a coherent state-of-the-art of diseases of the oral tract.

Going back in time, I find it striking to see how many scientists underwent their initial training in Dentistry but then moved on to make major contributions to health research, as well as to public health practice and policymaking. Some of my early teachers in Brazil, and several of the most competent statisticians, demographers, epidemiologists, and sanitarians I have known, indeed evolved from a clinical Dentistry background, having moved to Epidemiology and Public Health at later stages in their careers.

Despite the wide presence of dentists throughout epidemiological practice, a textbook of Epidemiology explicitly directed to the area of Oral Health was not yet available. This book definitely fills this large gap. Peres, Antunes, and Watt, with the support of their collaborators from many parts of the world, opted for an ambitious book—in the full sense of the word—which addresses three main approaches. The first part, "Oral Health Diseases and Disorders," follows the approach of disease-oriented Epidemiology, by reviewing the international literature on the frequency of more than a dozen outcomes relevant to oral health. These reviews are broad and systematic. They will certainly become essential readings for understanding the current situation of the distribution and determinants of dental diseases. The chapters also provide useful insights into present gaps in knowledge and on how these must be addressed, both by researchers and healthcare managers and policymakers.

Whereas the first part of the book canvassed the past and the present, its second part focuses on future challenges of Oral Health Epidemiology, being aptly named as "Hot topics in Oral Health Research." Persistent themes such as marked social inequalities—which are as prominent in oral health as in most other health conditions—are dealt with alongside topics of more recent interest, such as the influence of the life cycle, the use of big data, approaches, the evaluation of complex interventions, the impact of oral health on quality of life, and the relationship between oral and systemic diseases. This part also addresses ethical issues and topics related to the teaching of Epidemiology and its applications for health programs and policies. Thus, in its ambitious second part, the book provides an outstanding example to be followed by future Epidemiology compendia, regardless of their specific topic matter.

Finally, the third part, "Methods in Oral Health Research," provides the necessary tools for epidemiological practice, being aimed at building capacity in the conduct of their field research. Topics such as instruments for the gathering of data, validation of questionnaires, the validity of diagnostic tests, assessing and reporting bias, and systematic reviews of the literature are discussed. This part will undoubtedly become an essential read for undergraduate and postgraduate students interested in doing research in the field.

In summary, Peres, Antunes, and Watt were able to put together three books in one, describing the current situation of Oral Health Epidemiology, laying out the challenges for the future, and providing a toolbox that researchers must use to tackle these chal-

lenges. The role of scientific evidence in the diagnosis, planning, and evaluation of population health problems is deservedly receiving growing attention in recent years. This book will undoubtedly play a key role in improving the scientific basis of Oral Health worldwide.

Cesar Gomes Victora
Emeritus Professor of Epidemiology, Federal University of Pelotas, Pelotas, Brazil
Past President (2011–2014), International Epidemiological Association

Foreword

The new edition of the book *Oral Epidemiology* should be seen as a vital contribution to the efforts being made by the entire oral health community (students, researchers, academics, policy makers, NGOs…) that is dedicated to fighting against the burden of oral diseases and related oral health inequalities across the different regions of the world.

As comprehensively described in this excellent new book, the current oral health epidemiological situation is alarming. Oral diseases, as part of the noncommunicable diseases (NCD) burden, remain amongst the most prevalent conditions of mankind. Poor oral health causes millions of people to suffer from devastating pain, increases out-of-pocket financial burdens, and seriously affects the quality of life and well-being of people worldwide.

This situation must change. On the basis of the best available scientific knowledge, the book makes the case that effective and affordable solutions exist to respond more effectively to the oral health needs of populations. The burden of oral diseases and other NCDs can be reduced through public health interventions by addressing common risk factors, strengthening health systems and improving integrated oral health surveillance. In addition, the social determinants of health should be addressed to reduce oral health inequalities.

With this objective in mind, the World Health Organization is promoting the reinforcement of a public health approach to build on preventive population-based interventions and integrated patient-centered care. These strategies are aligned to the United Nations' Sustainable Development Goals (SDGs) that have set Universal Health Coverage (UHC) as a key societal target for improving health and well-being.

The book also presents the existing methodologies to be applied for reinforcing oral health information systems and integrated surveillance with other NCDs. Having good quality information on oral health is critical to demonstrate the scale and the impact of the problem and to monitor the impact of interventions in countries.

The World Health Organization has also a long tradition of epidemiological survey methodology to encourage countries to conduct standardized oral health surveys. Having readable, comparable, and sound epidemiological data is key for policy makers to enhance knowledge for better evidence-informed decision making in oral health policy development and implementation.

It is my hope that this comprehensive and high-quality book will help train a much-anticipated new generation of global oral epidemiologists in dental public health convinced of the need for interprofessional collaboration and with a thorough understanding of social dimension of health in order "to leave no one behind!"

Dr Benoit Varenne
Dental Officer, Global Oral Health Programme,
Noncommunicable Diseases Department, World Health Organization,
Geneva.

Contents

I Oral Health Diseases and Disorders

1 **The Contribution of Epidemiology to Oral Health Research** 3
Marco A. Peres, Jose Leopoldo Ferreira Antunes, and Richard G. Watt

2 **Global Burden of Oral Conditions** 23
Wagner Marcenes and Eduardo Bernabé

3 **Dental Caries** 39
Karen Glazer Peres, Marco A. Peres, and Jose Leopoldo Ferreira Antunes

4 **Epidemiology of Periodontal Diseases** 57
Vibeke Baelum and Rodrigo López

5 **Malocclusions** 79
Karen Glazer Peres, Paulo Frazão, and Carlos Flores-Mir

6 **Orofacial Pain** 107
Mario Vianna Vettore and Gabriela de Almeida Lamarca

7 **Dental Fluorosis: Epidemiological Aspects** 121
Loc G. Do and Diep H. Ha

8 **Traumatic Dental Injuries** 133
Carlos Alberto Feldens, Fernando Freitas Portella, and Paulo Floriani Kramer

9 **Epidemiology of Cleft Lip and Palate** 159
Kaye Roberts-Thomson

10 **Enamel Defects** 169
David J. Manton, Felicity Crombie, and Falk Schwendicke

11 **Oral Cancer** 193
Jose Leopoldo Ferreira Antunes, Tatiana Natasha Toporcov, Maria Gabriela Haye Biazevic, and David I. Conway

12 **Dental Erosion** 209
Karen Glazer Peres and Fabiana Vargas-Ferreira

13 **Tooth Loss** 223
Jun Aida

14 **Halitosis** 235
Paulo Nadanovsky

15 **Oral Lesions in Soft Tissues** 251
Sandra Beatriz Chaves Tarquinio, Marco A. Peres, Luísa Jardim Corrêa de Oliveira, and Karine Duarte da Silva

II Hot Topics

16 **Causal Inference in Oral Health Epidemiology** 267
Gustavo G. Nascimento and Benjamin W. Chaffee

17 **Socio-Economic Inequalities in Oral Health** 279
Ankur Singh, Jose Leopoldo Ferreira Antunes, and Marco A. Peres

18 **Life Course Oral Health Epidemiology** 295
Marco A. Peres, Karen Glazer Peres, Flavio Fernando Demarco, Marcos Britto Correa, and Anja Heilmann

19 **Sugar Consumption and Oral Health** 307
Anja Heilmann, Carolina Machuca Vargas, and Richard G. Watt

20 **Oral Health-Related Quality of Life** 319
Georgios Tsakos and Finbarr Allen

21 **Ecosocial Oral Health Epidemiology** 333
Samuel Jorge Moysés and Ankur Singh

22 **Use of Primary Care Settings to Collect Epidemiological Data** 347
Gill Davies and Iain A. Pretty

23 **Big Data and Machine Learning** 357
Stefan Listl and Alexandre D. P. Chiavegatto Filho

24 **Epigenetics in Oral Health** 367
Toby Hughes

25 **The Relationship Between Periodontal Diseases and Chronic Diseases** 379
Fábio Renato Manzolli Leite and Gustavo Giacomelli Nascimento

26 **Dental Health Services Epidemiology** 395
David Brennan

27 **Bioethics of Epidemiological Oral Health Studies** 409
Jonathon Timothy Newton

28 **Epidemiology, Politics, and Dental Public Health** 419
Carol C. Guarnizo-Herreño, Paulo Frazão, and Paulo Capel Narvai

29 **Water Fluoridation** 437
Andrew John Spencer

30 **Teaching Oral Epidemiology** 453
Richard D. Holmes and Georgios Tsakos

III Methods

31 **Measurement Instruments for Use in Oral Epidemiology** 465
João Luiz Bastos, Michael E. Reichenheim, and Claudia L. Moraes

32 **Reproducibility and Validity of Diagnostic Tests** 479
Renato Pereira da Silva, Andréa Videira Assaf, and Antonio Carlos Pereira

33 **Quantitative Bias Analysis in Dental Research** 495
Murthy N. Mittinty

34 **Reviews Systematic and Meta-analysis** 507
Roger Keller Celeste and Falk Schwendicke

Supplementary Information
Index 527

Editors and Contributors

About the Editors

Marco A. Peres
is a dentist, graduated in the School of Dentistry, University of São Paulo Brazil, with a PhD in Epidemiology. Marco was an Associate Professor of Department of Public Health, Federal University of Santa Catarina, Brazil (1995–2012), Director of the Australian Research Centre for Population Oral Health (ARCPOH), University of Adelaide, Australia (2012–2018), a Professor of Dental and Oral Health Research, School of Dentistry and Oral Health, Griffith University, Australia (2018–2020). Currently, Marco is a Professor at the National Dental Research Institute Singapore, National Dental Centre Singapore and Oral Health ACP, Health Services and Systems Research Programme, Duke-NUS Medical School, Singapore.

His research areas of interest include health services research, data linkage, oral health surveillance, use of fluorides, inequalities in oral health, life course epidemiology, and the relationship between oral health and general health. Marco is a founder member of the International Centre for Oral Health Inequalities Research and Policy (ICOHIRP) based at University College London, United Kingdom, a member of the Brazilian Commission of Social Determinants of Health and a member of the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, the deputy chair of the Expert Working Group for Fluoride of the Australian and New Zealand Nutrient Reference Values for Fluoride, a member of the Oral Health Expert Group of the Australian Burden of Diseases 2011 Study, and a member of the Australian Dental Association Oral Health Tracker Expert Group.

Marco is an internationally recognised researcher in the field of Population Oral Health and Oral Epidemiology, he has been cited in a paper published in 2016 in *Community Dentistry and Oral Epidemiology* (doi: 10.1111/cdoe.12249) as the seventh most productive researcher in Public Health Dentistry in the world in the last half-century. Marco was the recipient of the 2017 International Association for Dental Research (IADR) Distinguished Scientist Award for Global Oral Health Research. Currently Marco is the Vice-president of the IADR Global Oral Health Inequalities Research Network (GOHIRN).

Marco was on the Editorial Board of the *Community Dentistry and Oral Epidemiology* (2010–2012) and is currently Associate Editor of *Revista de Saude Publica/Journal of Public Health* (2015–) and *Brazilian Journal of Epidemiology* (2012–) and member of the Advisory Board of the *Australian Dental Journal* (2016–).

In the past 10 years, Marco has given oral presentations at 45 conferences in Australia, Brazil, the USA, the UK, Finland, Spain, Portugal, Italy, Poland, Canada, Uruguay, South Korea, Singapore, Japan, and Thailand.

Marco has supervised 38 Honours, Masters, and PhD students in Public Health, Dentistry and Epidemiology, authored three books, 15 book chapters, and more than 250 peer-reviewed papers. His work has received more than 13,000 citations, an H index of 65.

Jose Leopoldo Ferreira Antunes
is a sociologist, graduated at the University of São Paulo, Brazil, with a PhD in Social Sciences. Antunes is a Professor of Epidemiology, School of Public Health, University of São Paulo, Brazil.

His research areas of interest include dental health, oral cancer, epidemiological methods, and inequalities in health. Antunes is a member of the International Epidemiological Association, a member of the International Association of Dental Research, and a member of the Commission of Epidemiology at the Brazilian Association of Public Health.

Antunes is an internationally recognised researcher in the field of Population Oral Health and Oral Epidemiology. He was awarded Eminent Scientist of the Year 2003 (Brazil, South America), World Scientist Forum International Award of the International Research Promotion Council – IRPC, and Incentive Prize in Science and Technology "Successful Experiences of Incorporating Scientific Knowledge into Health Services" from the Brazilian Ministry of Health, 2008.

Antunes was on the Editorial Board of the *Community Dentistry and Oral Epidemiology* (2015–2017) and is currently at the Editorial Board of the *European Journal of Oncology Nursing* (2016–). He is also Associate Editor of *Oral Diseases* (2015–), and Editor-in-chief of *Revista de Saude Publica/Journal of Public Health* (2010–).

In the past 10 years, Antunes has taught courses on Epidemiology in Brazil, Colombia, Australia, and Spain, and has given oral presentations at international conferences and congresses worldwide.

Antunes has supervised 63 Masters and PhD students, and Post-Doctoral applicants in Public Health, Dentistry, and Epidemiology. He authored five books, 19 book chapters, and 210 peer-reviewed papers. His work has received more than 9,300 citations, an H index of 53.

Richard G. Watt
is a dentist who graduated from University of Edinburgh, UK, and then completed a MSc and PhD in Dental Public Health from University College London, UK. Richard is a Professor and Honorary Consultant in Dental Public Health, University College London, UK. He is the Director of the World Health Organisation, Collaborating Centre on Oral Health Inequalities and Public Health and is also Director of Research, Development and Innovation for Central North West London NHS Foundation Trust.

His main research interests focus on social and commercial determinants of oral health, inequalities in oral health and development and evaluation of community-based (oral) health improvement interventions. He provides expert advice on oral health policy to the UK Department of Health, NHS England, National Institute for Health and Care Excellence (NICE), and Public Health England. He has also provided policy advice to EU, FDI, and WHO oral health expert groups. He is the founder and lead of the International Centre for Oral Health Inequalities Research and Policy – a network of 55 researchers and policy makers from 17 countries. In 2014, he was awarded the IADR Distinguished Scientist Award for Behavioural, Epidemiologic and Health Services Research, and, in 2016, he gained the National Institute for Health

Research (NIHR) Senior Investigator Award, the only dentist in the UK gaining this recognition.

Richard has secured over £10.9 million in research grants from a wide variety of national and international funding agencies and has published 289 publications (peer-reviewed papers, books, and book chapters). In 2019, he lead the publication of a *Lancet* Series on Oral Health. Richard has delivered 108 international scientific presentations in a very diverse range of countries across the globe. He is currently on the editorial board of the *Journal of Dental Research*. He was previously Associate Editor for *Community Dental Health* and was on the editorial board of *Community Dentistry and Oral Epidemiology*.

At University College London, he was Director of the MSc in Dental Public Health (1992–2018) and has trained over 320 dental public health MSc students from all over the world. He has also supervised 21 PhD students.

Contributors

Jun Aida Department of Oral Health Promotion, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
j-aida@umin.ac.jp

Finbarr Allen Faculty of Dentistry, National University of Singapore, Singapore, Singapore
denpfa@nus.edu.sg

Jose Leopoldo Ferreira Antunes School of Public Health, University of São Paulo Faculty of Public Health, São Paulo, São Paulo, Brazil
leopoldo@usp.br

Andréa Videira Assaf Health Institute of Nova Friburgo, Universidade Federal Fluminense – UFF, Nova Friburgo, RJ, Brazil
avassaf@gmail.com

Vibeke Baelum Department of Dentistry and Oral Health, Oral Epidemiology and Public Health, Aarhus University, Aarhus, Denmark
baelum@dent.au.dk

João Luiz Bastos Department of Public Health, Federal University of Santa Catarina, Florianópolis, SC, Brazil
joao.luiz.epi@gmail.com

Eduardo Bernabé Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, London, UK
eduardo.bernabe@kcl.ac.uk

Maria Gabriela Haye Biazevic Department of Social Dentistry, School of Dentistry, University of Sao Paulo, São Paulo, SP, Brazil
biazevic@usp.br

David Brennan Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, SA, Australia
david.brennan@adelaide.edu.au

Paulo Capel Narvai School of Public Health, University of São Paulo, São Paulo, SP, Brazil
pcnarvai@usp.br

Roger Keller Celeste Department of Preventive and Social Dentistry, School of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil
roger.keller@ufrgs.br

Benjamin W. Chaffee Department of Preventive and Restorative Dental Sciences, School of Dentistry, University of California San Francisco, San Francisco, CA, USA
benjamin.chaffee@ucsf.edu

Alexandre D. P. Chiavegatto Filho Department of Epidemiology, School of Public Health, University of São Paulo, Faculdade de Saúde Pública, São Paulo, SP, Brazil
alexdiasporto@usp.br

David I. Conway School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
david.conway@glasgow.ac.uk

Marcos Britto Correa Graduate Program in Dentistry, Federal University of Pelotas, Pelotas, RS, Brazil

Graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, RS, Brazil
marcosbrittocorrea@hotmail.com

Felicity Crombie Melbourne Dental School, The University of Melbourne, Melbourne, VIC, Australia
Unknown_255@Meteor.com

Gill Davies Consultant in Dental Public Health (retired), Warrington, UK
gill.davies4@btinternet.com

Karine Duarte da Silva School of Dentistry, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
karineduartedasilva1@gmail.com

Renato Pereira da Silva Department of Nutrition and Health, Universidade Federal de Viçosa - UFV, Viçosa, MG, Brazil
renatop.silva@ufv.br

Gabriela de Almeida Lamarca Department of Community and Preventive Dentistry, School of Dentistry, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
gabilamarca@gmail.com

Luísa Jardim Corrêa de Oliveira School of Dentistry, Catholic University of Pelotas, Pelotas, RS, Brazil
luisa.oliveira@ucpel.edu.br

Flavio Fernando Demarco Graduate Program in Dentistry, Federal University of Pelotas, Pelotas, RS, Brazil

Graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, RS, Brazil
flavio.demarco@ufpel.edu.br

Loc G. Do Australian Research Centre for Population Oral Health, The University of Adelaide, Adelaide, SA, Australia
loc.do@adelaide.edu.au

Carlos Alberto Feldens School of Dentistry, Lutheran University of Brazil, Canoas, RS, Brazil
cafeldens@terra.com.br

Carlos Flores-Mir School of Dentistry, University of Alberta, Edmonton, AB, Canada
cf1@ualberta.ca

Paulo Frazão University of São Paulo, Public Health School, São Paulo, Brazil
pafrazao@usp.br

Carol C. Guarnizo-Herreño Department of Collective Health, School of Dentistry, Universidad Nacional de Colombia, Bogotá, Colombia
ccguarnizoh@unal.edu.co

Diep H. Ha Australian Research Centre for Population Oral Health, The University of Adelaide, Adelaide, SA, Australia
diep.ha@adelaide.edu.au

Anja Heilmann Research Department of Epidemiology and Public Health, University College London (UCL), London, UK
anja.heilmann@ucl.ac.uk

Richard D. Holmes School of Dental Sciences, Newcastle University, Newcastle upon Tyne, UK
richard.holmes@newcastle.ac.uk

Toby Hughes Adelaide Dental School, The University of Adelaide, Adelaide, SA, Australia
toby.hughes@adelaide.edu.au

Samuel Jorge Moysés Graduate Program, Life Sciences School, Pontifical Catholic University of Parana, Curitiba, PR, Brasil
s.moyses@pucpr.br

Paulo Floriani Kramer School of Dentistry, Lutheran University of Brazil, Canoas, RS, Brazil
paulokramer@hotmail.com

Stefan Listl Department of Dentistry – Quality and Safety of Oral Health Care, Radboud University – Radboudumc (RIHS), Nijmegen, The Netherlands

Medical Faculty, Department of Conservative Dentistry, Section for Translational Health Economics, Heidelberg University, Heidelberg, Germany
stefan.listl@radboudumc.nl

Rodrigo López Department of Dentistry and Oral Health, Section of Periodontology, Aarhus University, Aarhus, Denmark
rlopez@dent.au.dk; d.j.manton@umcg.nl

David J. Manton, BDSc, MDSc, PhD Centrum voor Tandheelkunde en Mondzorgkunde, Universitair Medisch Centrum Groningen, Groningen, The Netherlands
djmanton@unimelb.edu.au

Fábio Renato Manzolli Leite Department of Dentistry and Oral Health, Section of Periodontology, Aarhus University, Aarhus, Denmark
fabio@dent.au.dk

Wagner Marcenes Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, London, UK
marcenes.w@gmail.com

Murthy N. Mittinty School of Public Health, University of Adelaide, Adelaide, SA, Australia
murthy.mittinty@adelaide.edu.au

Claudia L. Moraes Department of Epidemiology, Institute of Social Medicine, Rio de Janeiro State University, Rio de Janeiro, RJ, Brazil
clmoraes.uerj@gmail.com

Paulo Nadanovsky Institute of Social Medicine, Rio de Janeiro State University and Department of Epidemiology, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
nadanovsky@ims.uerj.br

Gustavo Giacomelli Nascimento Department of Dentistry and Oral Health, Section of Periodontology, Aarhus University, Aarhus, Denmark
ggn@dent.au.dk

Jonathon Timothy Newton Clinical, Oral and Translational Sciences, Faculty of Dentistry, Oral and Clinical Sciences, Dental Institute, King's College London, London, UK
tim.newton@kcl.ac.uk

Antonio Carlos Pereira Department of Social Dentistry, Piracicaba Dental School, Universidade Estadual de Campinas – UNICAMP, Piracicaba, SP, Brazil
apereira111@gmail.com

Karen Glazer Peres National Dental Research Institute Singapore, National Dental Centre Singapore, Singapore

ACP Oral Health, Health Services and Systems Research Programme, Duke-NUS Medical School, Singapore, Singapore
karen.g.d.a.peres@ndcs.com.sg

Marco A. Peres National Dental Research Institute, National Dental Centre Singapore, Singapore

ACP Oral Health, Health Services and Systems Research Programme, Duke-NUS Medical School, Singapore, Singapore
marco.a.d.a.peres@ndcs.com.sg

Fernando Freitas Portella School of Dentistry, Lutheran University of Brazil, Canoas, RS, Brazil
portellaff@yahoo.com.br

Iain A. Pretty School of Dentistry, University of Manchester, Manchester, UK
Iain.A.Pretty@manchester.ac.uk

Michael E. Reichenheim Department of Epidemiology, Institute of Social Medicine, Rio de Janeiro State University, Rio de Janeiro, RJ, Brazil
michaelreichenheim@gmail.com

Kaye Roberts-Thomson Australian Research Centre for Population Oral Health, The University of Adelaide, Adelaide, SA, Australia
kaye.robertsthomson@adelaide.edu.au

Falk Schwendicke, MDPH, PhD Charité – Universitätsmedizin Berlin, Department of Oral Diagnosis, Digital Health and Health Services Research, Berlin, Germany
Unknown_9545@Meteor.com

Ankur Singh Centre for Health Equity, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia
ankur.singh@unimelb.edu.au

Andrew John Spencer Australian Research Centre for Population Oral Health, The University of Adelaide, Adelaide, SA, Australia
john.spencer@adelaide.edu.au

Sandra Beatriz Chaves Tarquinio School of Dentistry, Federal University of Pelotas, Pelotas, Rio Grande do Sul, Brazil
sbtarquinio@gmail.com

Tatiana Natasha Toporcov Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo, SP, Brazil
toporcov@usp.br

Georgios Tsakos Research Department of Epidemiology and Public Health, University College London (UCL), London, UK
g.tsakos@ucl.ac.uk

Carolina Machuca Vargas Department of Epidemiology and Public Health, University College London, London, UK

Population and Patient Health, Dental Public Health, King's College London, London, UK
carolina.vargas@ucl.ac.uk

Fabiana Vargas-Ferreira School of Dentistry, Department of Community and Preventive Dentistry, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
fabivfer@gmail.com

Mario Vianna Vettore Department of Community and Preventive Dentistry, School of Dentistry, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
m.vettore@sheffield.ac.uk

Richard G. Watt Dept. of Epidemiology and Public Health, University College London, London, United Kingdom
r.watt@ucl.ac.uk

Oral Health Diseases and Disorders

Contents

Chapter 1 **The Contribution of Epidemiology to Oral Health Research – 3**
Marco A. Peres, Jose Leopoldo Ferreira Antunes, and Richard G. Watt

Chapter 2 **Global Burden of Oral Conditions – 23**
Wagner Marcenes and Eduardo Bernabé

Chapter 3 **Dental Caries – 39**
Karen Glazer Peres, Marco A. Peres, and Jose Leopoldo Ferreira Antunes

Chapter 4 **Epidemiology of Periodontal Diseases – 57**
Vibeke Baelum and Rodrigo López

Chapter 5 **Malocclusions – 79**
Karen Glazer Peres, Paulo Frazão, and Carlos Flores-Mir

Chapter 6 **Orofacial Pain – 107**
Mario Vianna Vettore and Gabriela de Almeida Lamarca

Chapter 7 **Dental Fluorosis: Epidemiological Aspects – 121**
Loc G. Do and Diep H. Ha

Chapter 8 **Traumatic Dental Injuries – 133**
Carlos Alberto Feldens, Fernando Freitas Portella, and Paulo Floriani Kramer

Chapter 9 **Epidemiology of Cleft Lip and Palate – 159**
Kaye Roberts-Thomson

Chapter 10 **Enamel Defects – 169**
David J. Manton, Felicity Crombie, and Falk Schwendicke

Chapter 11 **Oral Cancer – 193**
Jose Leopoldo Ferreira Antunes, Tatiana Natasha Toporcov, Maria Gabriela Haye Biazevic, and David I. Conway

Chapter 12 **Dental Erosion – 209**
Karen Glazer Peres and Fabiana Vargas-Ferreira

Chapter 13 **Tooth Loss – 223**
Jun Aida

Chapter 14 **Halitosis – 235**
Paulo Nadanovsky

Chapter 15 **Oral Lesions in Soft Tissues – 251**
Sandra Beatriz Chaves Tarquinio, Marco A. Peres, Luísa Jardim Corrêa de Oliveira, and Karine Duarte da Silva

The Contribution of Epidemiology to Oral Health Research

Marco A. Peres, Jose Leopoldo Ferreira Antunes, and Richard G. Watt

Contents

1.1 Introduction – 4

1.2 Association and Causality – 4

1.3 Measures of Disease Frequency – 5

1.4 Typology of Designs for Epidemiological Studies – 7

1.5 Measures of Association – 8

1.6 Observational Studies – 10
1.6.1 Case Reports or Case Series – 10
1.6.2 Ecological Studies – 10
1.6.3 Time Series Studies – 11
1.6.4 Cross-Sectional Studies – 12
1.6.5 Case-Control Studies – 14
1.6.6 Cohort Studies – 15

1.7 Interventional (Experimental) Studies – 15
1.7.1 Clinical Trials – 15
1.7.2 Community Intervention – 19

1.8 Internal and External Validities – 19

1.9 Sources of Error in Epidemiological Studies – 19

1.10 Final Remarks – 21

References – 21

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_1

1

Learning Objectives

- To introduce core concepts and principles of epidemiology and its application to oral health research
- To discuss the different study designs and its utility to respond research questions
- To provide elements to identify potential sources of errors in epidemiological studies
- To demonstrate the indissociable link between epidemiology and public health

1.1 Introduction

Epidemiology has been conceptualised overtime in a variety of ways by a range of different authors. Porta [1] in a classic epidemiological text defined epidemiology as "the study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems". Two central assumptions support this definition and, therefore, epidemiology itself:

(i) The diseases, health conditions, and their determinants are not randomly distributed in population.
(ii) The knowledge of these factors has practical implications for the control and prevention of diseases and health problems.

Historically epidemiology has made an essential contribution in elucidating the causes of diseases and ways of tackling them. John Snow's investigation of the cause of the cholera epidemic in London [2], in the mid-nineteenth century, illustrates a notable and pioneering example of the contribution of epidemiology in solving health problems. By using his medical and statistical knowledge, along with his profound concerns over social issues, Snow provided helpful insights in how to prevent the disease, many years before Louis Pasteur formulated the principles of bacteriology and described the microorganism involved in the aetiology of the disease (*Vibrio cholera*).

In the twentieth century, particularly after the Second World War, the progress of epidemiology expanded its application beyond infectious diseases, allowing the study of non-communicable diseases, in the same time in which these diseases increased in their relative importance as a cause of morbidity and mortality. For instance, the Framingham Health Study (► http://www.framinghamheartstudy.org), a cohort study of over 5000 adults, which started in 1948 in the city of Framingham, Massachusetts, USA, led by the National Heart, Lung and Blood Institute; National Institute of Health; and Department of Health and Human Services; has contributed significantly to the understanding of the causes of heart diseases.

The combination of epidemiological studies, clinical observations and lab research constitutes the foundations in which health programmes and interventions, in its different specialties, are based. Other iconic examples of the use of epidemiology include the study which tested the efficacy of the polio vaccine developed by Jonas Salk, with over 1 million participants; the elucidation of the causal relationship between tobacco and lung cancer; the well-known Black Report [3], on socioeconomic inequalities in health in the Britain context; and the pioneering investigations on the mode of transmission of the HIV.

There are several classic examples of the use of Epidemiology in the field of oral health such as the contribution to the study of the effectiveness of water fluoridation to prevent dental caries, a measure considered as one of the top ten achievements in public health in the last century by the Centers for Disease Control and Prevention [4, 5]. The role of sugar on dental caries was elucidated by two classic studies which were carried out before the Helsinki Declaration, which would not be conducted under the current ethics guidelines [6]. The first was the Vipeholm study [7] (1945–1953), where patients of a mental hospital in Lund, Sweden, were exposed to a range of different sources of sugar to investigate the effect of consuming sugary foods of varying stickiness throughout the day on caries increment over 9 years. The second one was the Hopewood House study [8], conducted in New South Wales, Australia (1947–1962), which investigated the effect of a strict lacto-vegetarian diet that was low in sugar and refined flour on children's dental caries and subsequent rise of the disease after children's leaving the house.

This chapter aims to present a summary of the value of epidemiology in the oral health field. Conceptual, methodological, and analytical topics will be introduced in this chapter and discussed in greater depth in later chapters. We aim to demonstrate the utility of epidemiology for understanding and tackling the leading oral health problems globally by describing different examples of oral health studies that have been conducted around the world.

1.2 Association and Causality

Epidemiology seeks to explore the factors influencing patterns of disease and the distribution of health outcomes, as well as their underlying determinants. It is not a simple task to decide if some specific determinant is a necessary or sufficient cause or a protective factor for the specified disease. Epidemiology has tried to adopt practical ways to explore the epistemological complexity around the causality. Cause in epidemiology has been defined as an antecedent factor with potential for changing an outcome (the

effect). A cause is termed "necessary" when it must always precede an effect. This effect does not need to be the sole result of the specific cause. A cause is named "sufficient" when it inevitably initiates or produces an effect [1]. Therefore, in addition to temporally preceding the effect, the cause must also be associated with the outcome. Association is the relationship between two events, usually between an explanatory or independent variable (the exposure) and a health outcome, a dependent variable. Exposure is the quantity or intensity of a factor which supposedly causes a disease (or health outcome) [9]. An association is positive if two events or variables have the same direction; for example, they increase concomitantly. The association is negative when indicating the opposite direction between the events or variables.

Not all statistical association is a causal association. Judging whether a variable is causal or is not is a complex task. Although this is a controversial issue, some conditions and criteria should be taken into account, as proposed by Hill [10]:

- The strength of association: strong associations are more likely to be causal.
- Consistency: repeated observations of a particular association in different populations, in different contexts.
- Specificity: one cause leads to one particular event. This assumption was based on the unicausal theory and has since been heavily criticised.
- Temporality: it is mandatory that the postulated cause precedes the effect.
- Biological gradient: the existence of a dose-response relationship, when an exposure increases, the risk of the outcome also increases.
- Biological plausibility: the observed associations should be explained based on available knowledge.
- Coherence: the interpretation of a causal association should not contradict the natural history of the disease and its biological aspects.
- Experimental evidence: Are randomised clinical trials available? For etiological studies, this principle is unpractical for ethical reasons.
- Analogy: Are there similar associations?
- Reversibility: The removal of a factor implies a reduction in the number of cases of a disease or health outcome.

An updated approach of causality is found in ▶ Chap. 16, Part II.

1.3 Measures of Disease Frequency

To perform epidemiologic studies, it is necessary to measure the frequency and distribution of ill-health in populations. One of the most basic ways to accomplish this is to gauge the absolute number of specific events such as registered cases of the disease or its associated deaths. For example, the International Agency for Research on Cancer (IARC) estimated that the total number of deaths due to oral cancer accounts for 177,384 (67% in males) in 2018 [11]. However, depicting absolute numbers may lead to a misinterpretation of the risk of disease, given the variations in the populations under risk, in other words, the denominator. The same number of cases of the disease has different meanings according to diverse populations, for example, for two cities with a different number of inhabitants.

In this sense, epidemiologic data analysis rarely uses absolute numbers but coefficients, ratios, and proportions to make comparisons possible. Moreover, the epidemiological analysis commonly requires standardisation of coefficients to allow comparisons between populations with different characteristics, such as the distribution by gender and age. The ratio is the quotient of a number divided by another. Rate, proportions, and percentage are types of ratios. According to the Dictionary of Epidemiology [1], "the numerator of a proportion is included in the population defined by the denominator, whereas in other types of ratios the numerator and denominator are distinct quantities, neither being included in the other". This is the case of the odds, the ratio of the probability of occurrence on an event in relation to the probability of non-occurrence. The rate is an expression of the frequency with which an event occurs in a defined population, usually in a specified period.

As far as morbidity measures are concerned, there is a distinction between prevalence and incidence. The former quantifies the proportion of individuals with disease in a given population, place, and time. The formula for the calculation of prevalence is:

> Prevalence = number of cases of disease or health outcome/ population is a specific place and time.

Figure 1.1 shows the prevalence of tooth loss among adolescents in Brazil. In this case, the denominator is composed of people aged 15–19, while the numerator is formed by those with at least one missing tooth, expressed in percentage.

In contrast to prevalence, the incidence is a measure of new cases of disease or health outcomes during a period of time. Two related measures are used in this regard: the incidence proportion (cumulative incidence) and incidence rate.

A useful way to think about cumulative incidence (incidence proportion) is that it is the probability of developing the disease over a fixed period; as such, it is an estimate of

1

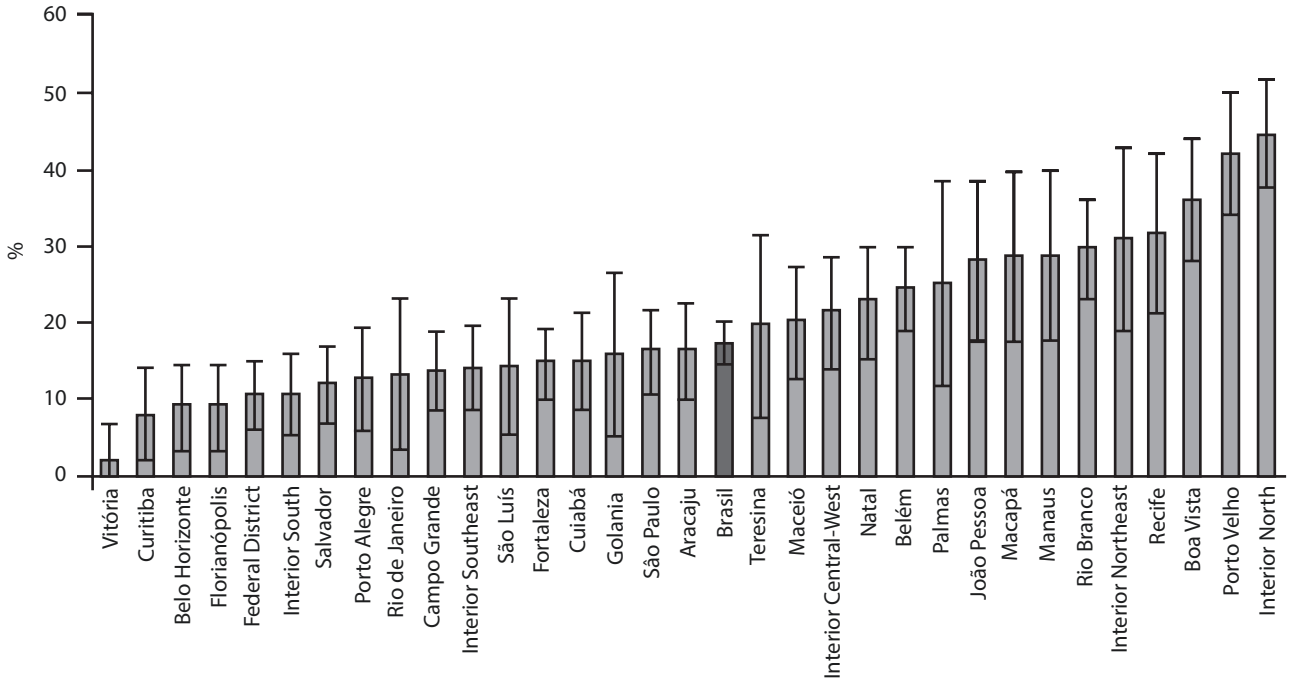


Fig. 1.1 Prevalence of teeth lost in individuals aged 15-19, according to domain (state capitals and interior). SB Brasil 2010. (Source: Peres et al. [12])

risk. Kenneth Rothman [9] used the example of a newspaper article saying that women who are 60 years of age have a 2% risk of dying from cardiovascular disease. As written, this statement is difficult to interpret, because it does not specify a period. In order to interpret the risk, it is necessary to know the length of time that it applies. A 2% risk has a very different meaning if it is over the next 12 months vs. the next 10 years. This measure assumes that the entire population at risk at the beginning of the study period was followed for a specified period. By definition, the whole population under observation is free from the disease at the beginning of the period, and its values can range from 0, indicating no new cases in the period, to 1 (or 100%), a hypothetical reference regarding the acquisition of the disease by the entire population in the period. The population, in this case, is fixed, and it cannot be added to new elements during the period of follow-up [13].

Scheutz [14] exemplifies the use of this measure through a study to determine the risk of developing oral candidiasis in 123 HIV-positive individuals, followed up for 3 years. All subjects were free of candidiasis at the beginning of the follow-up. After 3 years, candidiasis was diagnosed in 21 individuals. Considering that all the subjects investigated remained in the study throughout the follow-up time, the cumulative incidence in this period was calculated as 21/123 = 0.17 or 17%. In this case, the estimated risk of developing candidiasis in this population was 17% in 3 years.

However, there are situations in which the population exposed to risk (the denominator) is not fixed (open population), because people can enter or leave the observation for varying periods. Even if all individuals come into the study in the same observation period, the exposure time of each may not be uniform until the end of the study for several reasons. There may be a loss of information, an occurrence of disease (the individual gets into the numerator), migration, or death. Everyone contributes to a specific time of exposure without the disease, and, therefore, the denominator becomes no longer the individual, but rather the time that each one remained in observation without the disease. For example, 100 individuals in observation for 1 year are equivalent to 100 person-years or the same as 200 individuals under observation for 6 months. That is, this concept introduces the notion of people-time of exposure that becomes the denominator. This measure takes into account the number of individuals in a population that becomes ill, as well as the length of time contributed by all persons during the period they were in the population. Every member of the population experiences a specific amount of time in the population over the risk period; the sum of these times considering all population members is termed the total *person-time* at risk over the period [9].

Cumulative incidence = the number of new cases of a specific outcome within a particular length of time/population under risk at the beginning of the period

Incidence rate = number of new cases of a specific outcome within a particular length of time/∑ person time spent in population without the outcome

Prevalence and incidence measure the frequency and distribution of a particular event, informing us of the magnitude of the health problems in the population. They allow the comparison of health situations in different regions, according to demographic and social characteristics, and at different periods, thus informing health planning.

Prevalence, incidence, and time of observation are interrelated factors. Prevalence depends on the incidence rate and duration of the disease. If the incidence is low, but the affected individuals present the condition for an extended period, the proportion of the population presenting the disease at a particular point in time may be high in comparison to the incidence rate. On the other hand, if the incidence rate is high, but the duration of the disease is brief, with rapid recovery or even death, the prevalence will be low concerning the incidence. Thus, through these forms of measurement, and in conjunction with the mortality rate, the lethality (fatality) coefficient can be assessed.

For example, at the beginning of the AIDS epidemic, when the disease began to be recognized and diagnosed, despite its high incidence, the prevalence was low, because the disease was lethal in a relatively short period. Chronic diseases, such as diabetes, provide an alternative example, for which the long course of the disease determines lower values of incidence than of prevalence.

1.4 Typology of Designs for Epidemiological Studies

Epidemiological studies can be classified according to different perspectives, and it is not always possible to establish consensus on the forms of classification. The first modality of classification of epidemiological studies refers to the scope of its objectives. The precise definition of the objectives is a fundamental condition for the planning of any study. The type of study is a consequence of the research objectives. The study is descriptive when the researcher solely intends to describe the pattern of the occurrence of diseases with variables related to the person, time, and place. When specific hypotheses of causal association between variables are tested, the study is said to be analytical. At the intersection between these two types, it is said that the study is exploratory when the study of associations between variables complements the description, but in a way not aimed at proving specific hypotheses.

Epidemiological studies are also classified according to their methodological aspects, with particular reference to the mechanisms used for data collection and the form of their organisation in time. In this respect, a first distinction could be established between experimental, or intervention studies, and observational studies.

Experimental studies differ from observational studies because the researcher is intervening in the studied population, controlling some exposure effect. These studies seek to test causal hypotheses about associations involving interventions of interest, such as the use of medications or vaccines, techniques, or preventive methods. Among these studies, the "randomised clinical trials" (RCTs) is often considered as the "gold standard" and the most reliable resources to produce evidence in health, in general, with repercussions even in journalistic media.

In turn, observational studies are those in which the researcher does not intervene, that is, does not artificially introduce an exposure factor and only reports the data that could be gauged through observation. They are mainly used to assess the aetiology of the phenomena. It is important to emphasise that both experimental and observational studies should be subject to a careful institutional evaluation regarding the ethical precepts of research involving human beings since it is easy to perceive that both may involve risks to the participants investigated.

Randomised studies are controlled, because the random allocation of the intervention in a large number of individuals (required sample) results in statistically equal probability of the frequency of the characteristics of the individuals in the groups exposed to intervention and control (without intervention), such as gender, age, socioeconomic status, frequency and quality of toothbrushing, etc. On the other hand, when this does not occur, it is said that the studies are uncontrolled. In the context of intervention studies, when the investigator lacks full control over the allocation or timing of intervention but conducts the study as an experiment, it is said that the study is not randomised, i.e. it is a quasi-experiment [1]. These indications can be synthesised in ◘ Fig. 1.2, based on the proposition of Grimes and Schulz [15].

As for the form of organisation of data in time, studies can be classified in cross-sectional or longitudinal. Cross-sectional studies are those involving an instantaneous point in time. For reasons of ease of data collection, both the exposure factors and the outcomes considered are evaluated simultaneously. Therefore, it is excluded, in most cases, the possibility of establishing temporal connections between the studied variables. Cross-sectional studies can be simple, when they involve a single temporal data collection or are composed of two or more successive data collections, a modality also known as "Panel Studies".

1

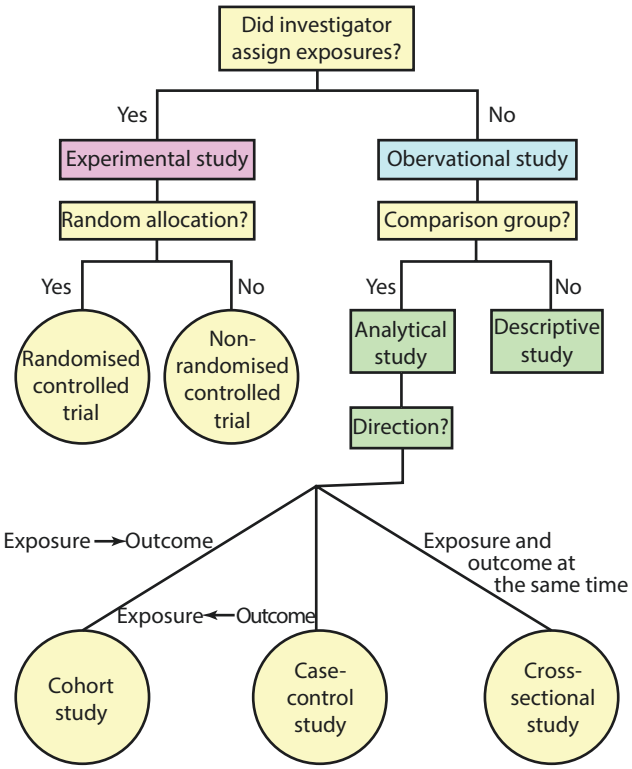


Fig. 1.2 Types of epidemiological study designs. (Reproduced from The Lancet [15], with permission of Elsevier)

In longitudinal studies, data collection is organised over time. The gathering of data may be "retrospective" or "prospective", depending on the temporal flow considered. Although there are notable exceptions, in general, cohort studies are prospective. That is, data from a given population cohort are collected over time while case-control studies are retrospective. Once differentiated the subjects integrated into the case group (with the outcome) and the control group (without the outcome), the goal is to collect information about the possible exposure factors that have occurred in the past. As for experimental studies, it is easy to perceive that they should be prospective, because the intervention cannot be done before data collection, and it is necessary to wait for the time programmed for its effects to be noticed.

1.5 Measures of Association

Many epidemiological studies have the objective of evaluating the association between exposures (risk factors or protection) and an outcome, for this purpose, association measures that can be expressed in different forms. In the case of categorical variables, contingency tables constitute a viable resource for calculating these measures. In its purest form, contingency tables (which classify the population quotas according to characteristics of the exposure and the effect considered) have two rows and two columns and are referred to as the fourfold or 2 × 2 table (Table 1.1).

Table 1.1 Form of contingency tables for the presentation of epidemiological data

Exposed	Disease +	Disease –	Total
Yes	a	b	$a + b$
No	c	d	$c + d$
Total	$a + c$	$b + d$	$a + b + c + d = N$

Cohort, clinical trials and cross-sectional studies try to respond the following question:

$$a/(a+b) > c/(c+d)?$$

However, for Case-Control Studies the formulated question is: $a/(a + c) > b/(b + d)$?

As shown in Table 1.1, a represents the number of individuals exposed and sick; b represents the number of individuals exposed and not sick; c is the number of individuals who are not exposed and who are sick; and, lastly, d indicates non-exposed and non-diseased individuals. In addition to these values, the table displays the partial totals in each row or column:

$a+b$ = total of exposed individuals;

$c+d$ = total of unexposed individuals;

$a+c$ = total of sick individuals; and

$b+d$ = Total non-diseased individuals.

Based on data from contingency tables, it is possible to calculate different measures of association between variables related to exposure and disease measures. The relative risk (RR) indicates the risk of the disease among those exposed about the risk of the disease among the non-exposed. The following formula expresses its arithmetic expression:

$$RR = Ie / Io$$

Being:

$$Ie(\text{incidence of the disease in the exposed}) = a/(a+b); \text{ and}$$

$$Io(\text{incidence of the disease in the non-exposed}) = c/(c+d).$$

RR values higher than 1 are obtained when the incidence in the exposed group is higher than the incidence in the non-exposed, suggesting that exposure is a risk factor. RR values lower than 1 are obtained when the incidence in the exposed is lower than in those not exposed, indicating that exposure is a protective factor. Additionally, when RR equals 1, the incidence in the exposed will be equal to the incidence in the non-exposed, indicating no association between the disease and exposure. For hypothesis testing, biostatistics provide different resources such as the Fisher's exact test, the chi-square test, and the estimation of confidence intervals, which are the most common analytical modalities for application in the assessment of contingency tables.

The same elements used in the calculation of the relative risk can be rearranged to estimate other quantities of epidemiological interest, explicitly aimed at quantifying how much of the risk can be attributed to the exposure considered. The attributable risk (AR) refers to the proportion of the disease among the exposed ones that can be considered related to the exposure. Thus, AR indicates the burden of disease in an exposed population that can be prevented by the elimination of exposure, and the formula for its calculation can be given by the expression:

$$\text{AR}\% = \left[\left(\text{Ie} - \text{Io}\right)/\text{Ie}\right] \times 100, \text{expressed in percentage; or}$$

$$\text{AR} = \text{Ie} - \text{Io} \text{ expressed in absolute values.}$$

The population attributable risk (PAR) measures the excess of the disease rate in the population that is attributable to the exposure:

$$\text{PAR} = \left[\left(\text{Ip} - \text{Io}\right)/\text{Ip}\right] \times 100, \text{ being}$$

$$\text{Ip} = \text{incidence in the population} = \left(a + c\right)/N \; [13, 16]$$

As the calculation of the incidence measures demands the organisation of the data in time, the risk measures, i.e. relative risk, attributable risk, and population attributable risk, must be estimated in prospective longitudinal studies, i.e. interventional and cohort studies.

For example, in a cohort study on oral health, the population attributable risk of early infant conditions (deficit in the height-for-age ratio at 12 months of age) was evaluated for the occurrence of dental caries in permanent dentition at 12 years of age and in the deciduous dentition at 6 years of age. The population attributable risk for having caries at 12 years was 3.1% for the height-for-age deficit and 64.9% for caries in the deciduous dentition. This result means that in case the mentioned risk factor was eliminated, we would have a reduction of 3.1 and 64.9% in the occurrence of caries in the 12- and 6-year-old population, respectively [17].

There is another measure of association that can be used in cross-sectional and longitudinal studies: the odds ratio (OR), whose mathematical expression is as follows:

$$\text{OR} = \left(a/c\right)/\left(b/d\right) = ad/bc$$

The odds are the ratio of the probability of occurrence of an event to that of non-occurrence. For example, if 70% of those who smoke develop periodontal disease, 30% do not develop the condition. The odds between smokers and non-smokers for the occurrence of periodontal disease are 70/30 or 2.3. This measure indicates that the chance of developing periodontal disease is 2.3 times higher among smokers than among non-smokers.

For cross-sectional studies, in addition to the odds ratio, it is still possible to calculate the prevalence ratio (PR), comparing the measure of prevalence obtained for both groups, with and without exposure. Although it is a controversial topic, some authors advocate the use of PR in cross-sectional studies where the outcome (dependent variable) is relatively frequent (higher than 15%), because in this case, the OR tends to overestimate the PR [18].

For case-control studies, on the other hand, the database comprises two independent samples, one for the cases (affected by the outcome) and the other for the controls (not affected by the outcome). Independent samples cannot be summed up, and the last column of totals, in Table 1.1, is not applicable. Therefore, neither the incidence nor the prevalence ratio is applicable in case-control studies. For this type of research, the odds ratio is the measurement of association of choice.

Table 1.2 summarises, for each type of epidemiological study, the preferable measures of association between categorical variables, whose calculation can be made using the data depicted in contingency tables. This synthesis has only an introductory character, and it is

Table 1.2 Epidemiological study design, the form of analysis, and association measures

Study design	Form of analysis	Association measures
RCT	Incidence in the exposed/ incidence in the non-exposed	RR
Cohort	Incidence in the exposed/ incidence in the non-exposed	RR
Case-control	Chance of being exposed in the cases/chance of being exposed in the controls	OR
Cross-sectional	Prevalence in the exposed/ prevalence in the non-exposed	OR or PR

noteworthy that different more complex modalities of analysis can be derived for specific purposes, for example, when it is necessary to consider the simultaneous effect of two or more factors of exposure on the same outcome (multivariate analysis) or when the factors of interest are not being measured categorically and quantitatively (parametric analysis).

1.6 Observational Studies

Observational studies can be descriptive, exploratory or analytical. Descriptive studies are essential in the field of public health, for administrators and health policymakers, because they identify which groups of the population are more or less affected by health problems and inform decisions on the allocation of resources. Descriptive studies use information routinely collected as census data, records of vital statistics on births and deaths, data from health services, or data that were specifically collected for registering the distribution of a given disease or health condition. Usually, observational studies are a first step towards the elucidation of health determinants [13].

Grimes and Schulz [19] compared descriptive studies to journalistic reports and identified five questions they should address:

1. Who? What are the characteristics of the individuals or population surveyed, such as income, schooling, gender, age, and others?
2. What? What is the condition studied? This type of study needs a precise case definition, the forms of diagnosis, and its measures.
3. Why? Descriptive studies should provide clues about the causes that can be elucidated in future research with more appropriate design.
4. When? The temporal aspects indicate information and clues about the event in question. Was there a seasonal or cyclical variation? Did the distribution of the disease in question have an increasing or decreasing trend? Was it levelled off?
5. Where? How does the distribution of the event differ according to the regions of a country, state, or city?

1.6.1 Case Reports or Case Series

A relatively simple type of epidemiological study relates to the reporting of one or more cases or even a series of cases. As indicated by the name, this is a detailed description of a certain number of manifestations of the disease, reporting in depth the characteristics of interest that may suggest etiological hypotheses and represent an essential interface between clinical and epidemiological studies [13].

An example of historical value for oral health research can be provided by the curiosity of Frederick McKay, a dentist from Colorado Springs, USA, who reported cases of patients with mottled enamel in the early twentieth century. The record of his observations contributed to the subsequent undertaking of the epidemiological research that explored the relationship between fluoride, fluorosis, and dental caries which was conducted by Henry Trendley Dean (1893–1962) [20] and is further explained in ▶ Chap. 7, Part I and ▶ Chap. 29, Part II.

1.6.2 Ecological Studies

Ecological studies, aggregated data studies, or georeferenced correlation studies are those that use information measured for population groups and not for individuals. As an example of an ecological study, Screeby

[21] reported a strong correlation between the average DMFT index at 12 years and the supply of sugar in 47 countries. Both the exposure factor (sugar) and the outcome (caries) were measured at the population level, with data aggregated to the participating countries (◘ Fig. 1.3).

In ecological studies, the description and analysis are referred to the average exposure and the prevalence or rate of disease in the participating geopolitical units [22]. As an example of geographic application in ecological studies of analytical nature, Antunes et al. [23] investigated the association between dental caries and dental treatment needs of schoolchildren aged 5 and 12 years with levels of social development of each of the districts of the city of São Paulo and indicated differential levels of risk for the development of the disease. ◘ Figure 1.4 indicates that the lowest caries indices were measured in the central portion of the city, whereas the more distant and impoverished areas of the city periphery presented progressively higher risk indicators of the outcome.

Ecological studies have some critical advantages over individual-based studies. Often, it is precisely to explain the contextual effects on the prevalence of disease. There are often limitations of individual measures to allow for other analytical assessments. Also, aggregated data studies have lower cost and analytical simplicity and are easy to conduct from an ethical standpoint. Finally, some exposures can only be measured in the population without correspondence at the individual level, for example, the Human Development Index of a region or municipality.

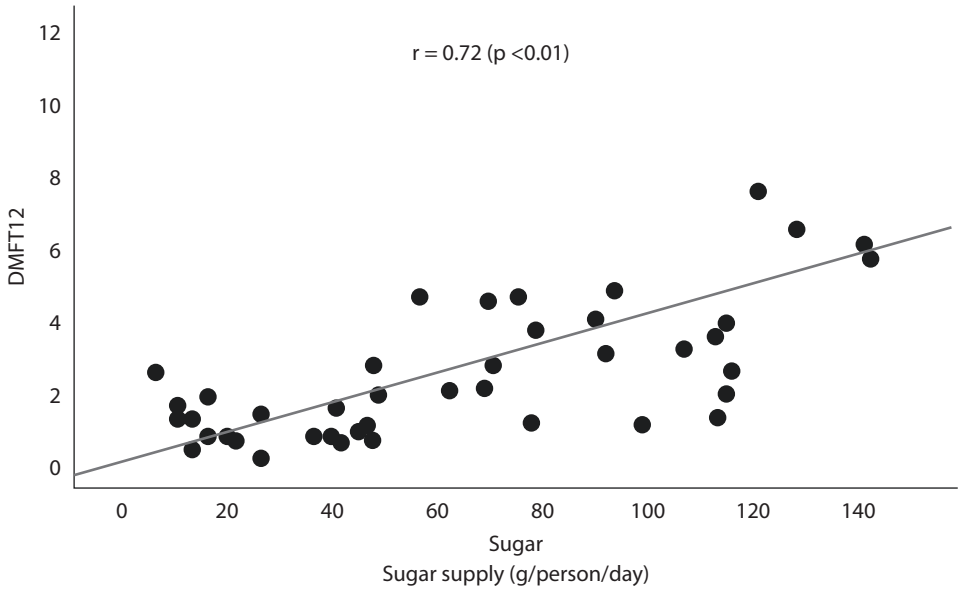


Fig. 1.3 Average DMFT index of 12-year-old children according to the supply of sugar in 47 countries [21]

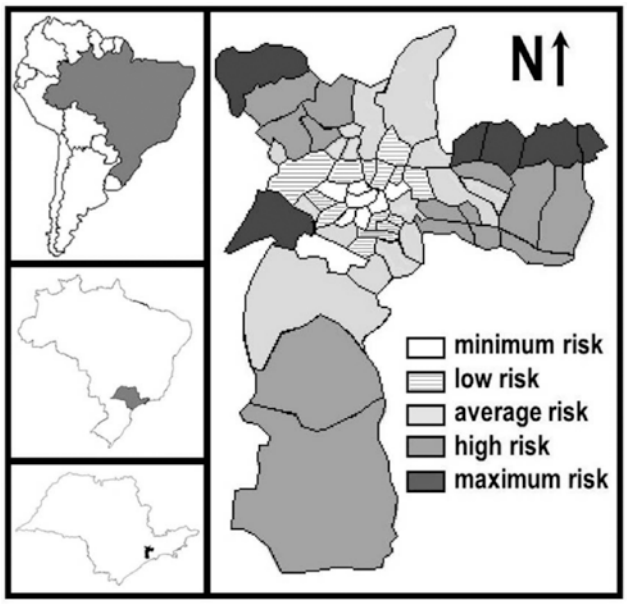


Fig. 1.4 Estimation of caries risk in 5–12 years old schoolchildren in São Paulo, 1996, and the inset of the city in the State of São Paulo, Brazil, and South America [23]

The main limitation of the ecological study refers to the impossibility of inferring to the individual level the results obtained at the population level (ecological fallacy). However, this limitation is not inherent to the characteristics of this type of study; most often it occurs due to the researcher's misconceptions when planning and reporting an ecological study with the purpose of establishing individual risk or interpretation of unfamiliar readers. Another problem concerns the difficulty in controlling the possible confounding effect of factors not modelled at the level of aggregation of the study [13]. However, Morgenstern [22] draws attention to the fact that these characteristics do not disqualify this type of study, but only highlight its limits in terms of applicability. Ecological studies are beneficial for evaluating policies, programs, and interventions in health.

1.6.3 Time Series Studies

Time series studies constitute a unique form of aggregated data studies, in which aggregation is performed not in different geographic contexts in a single reference period but a single geographic region of reference and in different periods.

Time series analysis seeks to identify patterns of regularity in the variation of the variables under investigation. In epidemiological studies, the search for these regularity patterns addresses three preferential items: first, the temporal progression, involving the understanding of the forms of temporal variation of the measures of interest; second, the concomitant variations of other population characteristics of interest; and third, the prediction of the most immediate future pattern of these variables.

Regarding the temporal dimension, what is sought to identify are the trends (global or partial) of the evolution of the series; cyclical variations; seasonal variations; and random variations. "Trend" is the part of the temporal series that reflects a regular movement of a different format but persistent in some direction, the increase, the decline, or the stationary character of the values. The cyclic and seasonal components identify

1

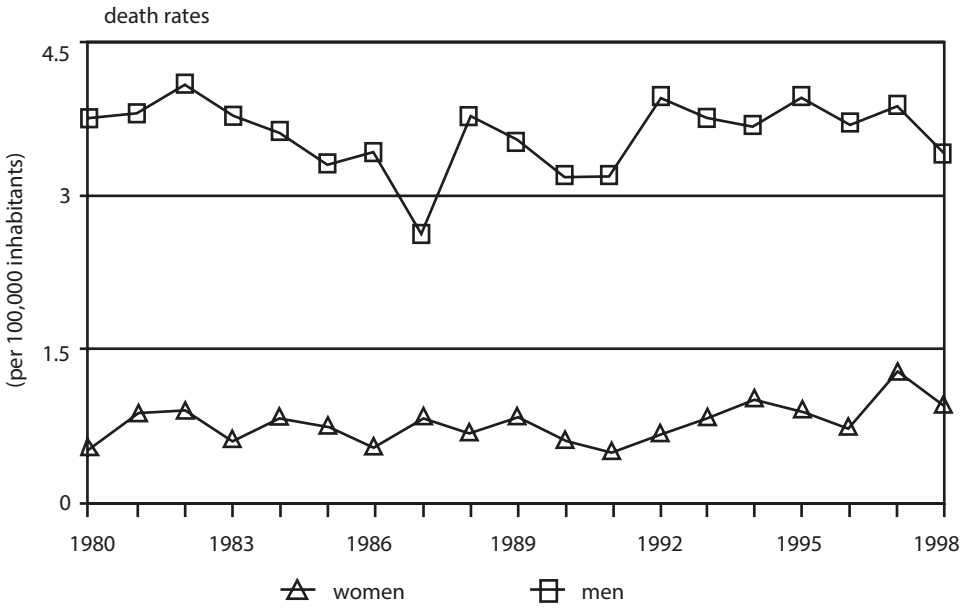


Fig. 1.5 Temporal series of oral cancer mortality rates in the city of São Paulo in the period 1980–1998 standardised by age, according to gender [25]

relatively regular movements around the delineated trend, differentiated by the frequency of variation. Cyclical movements are configured over the years; the seasonal movements are often of a smaller scale, and they are generally associated with the seasons and can be measured in months or weeks. The random component reflects disturbances caused by factors that do not repeat regularly. All these components can be recognised and quantified by the modern methodologies of statistical analysis, and Fig. 1.5 presents examples of time series studies with a stable trend, an absence of cyclic variation, and a presence of a random variation.

The correlation between the modelled temporal series and other chronologically organised variables seeks to verify whether the hypotheses suggested (to explain, e.g. the increase or decrease in mortality due to a specific disease) corresponds to concomitant variations in other population characteristics of interest.

Finally, concerning the predictive analysis, its aim is obtaining the best estimation of its future pattern, based on the progression of the values, thus informing the planning of services, public health programmes, and targeting collective efforts [24].

1.6.4 Cross-Sectional Studies

Cross-sectional studies are epidemiologic research whose objective is to describe the health conditions of a given population in a given area and time, without including the study of the aetiology of a given event. This definition is valid even when the objective of these studies is to test associations between the distribution of health outcomes and exposure factors. In other words, cross-sectional studies have an exploratory or analytical nature; they are not only descriptive.

Its denomination – "cross-sectional study" – derives from the fact that information on both the outcome and exposure is collected at the same point in time. When the aim is to describe the disease in a given location, these studies are referred to as epidemiological surveys, a type of research that is often used in oral health.

Cross-sectional studies are analytical when it aims to assess associations of interest, even if this association is not assessed in chronological order. For example, the study by Peres et al. [26] evaluated the association between periodontal disease and socio-demographic characteristics of Brazilian adults, in particular, to test the hypothesis that periodontal disease occurs more frequently in adults self-reported as Blacks and *Browns*. Racial classification in Brazil relies primarily on skin colour or physical appearance. The question for "Skin Colour" in Brazilian Censuses has usually response options of "White," "Black," "Yellow" (Asiatic), "Brown" ("pardo"), or "Indigenous." Based on their data, Table 1.3 indicates that self-reported Black and Brown adults, males, of lower schooling and income, have a higher prevalence of periodontal diseases than whites, women, and individuals with higher schooling and income. Cross-sectional studies, even those classified as analytical, are relatively simple to perform, low-cost, and fast; do not require the follow-up of people over time; and are useful for the evaluation and planning of health services.

As the main limitation to cross-sectional studies, it should be considered, in most cases, the impossibility of establishing the temporal nexus necessary for the proof

Table 1.3 Multivariable assessment of periodontal disease and socio-demographic characteristics of Brazilian adults. Brazil, 2003 (n = 11.342) [26]

Variables	Prevalence (95%CI)	Adjusted OR (95%CI)
Skin colour		
White	7.2 (5.7;8.8)	Reference
Brown	10.1 (8.4;11.9)	1.5 (1.2;1.8)
Black	11.8 (8.8;14.9)	1.6 (1.2;2.1)
Gender		
Females	7.9 (6.6;9.2)	Reference
Males	11.1 (9.3;12.9)	1.5 (1.2;1.7)
Age (years)		
35–39	7.8 (6.5;9.1)	Reference
40–44	10.5 (8.9;12.1)	1.4 (1.2;1.6)
Educational level (years)		
≥ 12	5.1 (3.6;6.5)	Reference
9–11	7.1 (5.7;11.3)	1.3 (1.0;1.8)
5–8	9.5 (7.7;11.3)	1.6 (1.2;2.1)
≤ 4	10.5 (8.8;12.2)	1.5 (1.1;2.1)
Per capita income (Brazilian reais)		
≥ 200	6.0 (4.6;7.4)	Reference
101–199	8.5 (6.8;10.2)	1.3 (1.1;1.7)
51–100	10.6 (8.7;12.6)	1.7 (1.3;2.1)
≤ 50	10.8 (8.8;12.8)	1.7 (1.3;2.1)

of hypotheses involving causes and effects, since both are collected at the same time. Moreover, information regarding the current exposure may be substantially different from the past exposure, and this factor may be particularly relevant when investigating chronic diseases. Other limitations relate to the possibility of underestimation of the associations evaluated, due to the absence of data on individuals who died or who, having been cured, eventually ceased to be considered in the study. Lastly, it is essential to underscore that these studies do not allow the direct calculation of incidences and therefore of the relative risk. However, it is possible to estimate risk through other measures of association such as the odds ratio and the prevalence ratio [13]. Some of the limitations as mentioned above can be overcome by current cut-edging counterfactual analytical approaches as presented in ▶ Chap. 1, Part II.

To overcome these problems, at least in part, different strategies can be adopted. One of these is the realisation of two or more successive cross-sectional studies, configuring the so-called "Panel Studies". Peres et al. [27]. used data from nine successive National Dental Telephone Interview Surveys (NDTIS) from 1994 (n = 6907) to 2013 (n = 6778) performed in Australia among individuals aged 15 years or over. The outcome was comprised of those participants who reported they had a toothache very often, often, or sometimes during the last 12 months. Repeated studies with the same characteristics have been performed as depicted in Fig. 1.6.

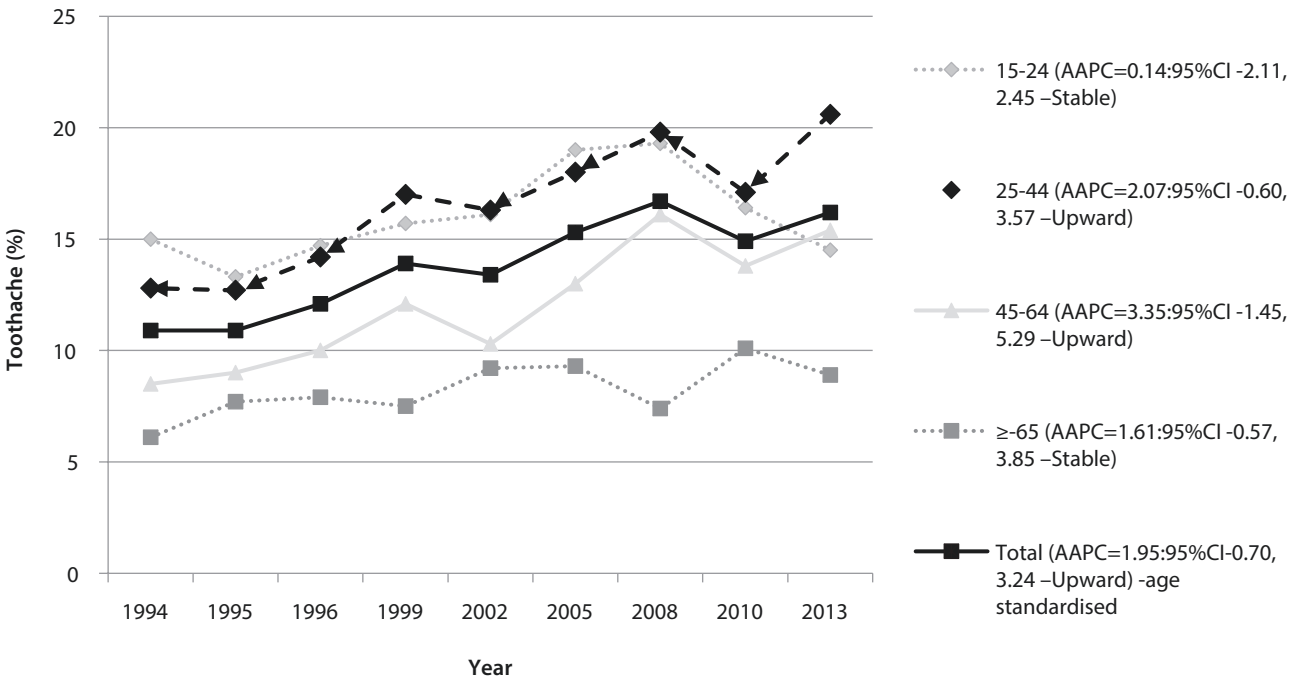


Fig. 1.6 Time trend analysis for toothache prevalence, according to age groups. NDTIS, 1994–2013, Australia [27]. (AAPC: the average annual percentage change)

1

1.6.5 Case-Control Studies

Case-control studies refer to a modality of longitudinal observation. It begins with the selection of a group of individuals with the disease or health condition that is intended to study (cases) and one or more groups (control), comprised by individuals who have not the same health outcome and who are from the same population of the cases. From a logical point of view, the study starts with the manifestation of the outcome, and it aims to investigate the differential effect of several causal factors to which both groups were differentially exposed in the past. In this sense, it is said that case-control studies are retrospective.

The selection of the control group is a critical point of case-control studies. The definition of the population source is of fundamental importance for this type of study, and it determines the population from which the control sample should be recruited [9]. There are different strategies for the selection of controls, each with advantages and disadvantages, from the operational point of view and consequences for the inference of results. In general, it is recommended that controls are selected from the general population (population-based studies), from neighbours, relatives, or companions to the health service in which the cases were attended and hospital controls recruited in the same health unit.

The controls should be similar to the cases in most of their characteristics so that the comparison of the differential effect of the exposure factors can be referred to their fundamental difference, which is being or being not affected by the disease or health condition investigated. When one or more exposure characteristics are controlled for the allocation of research subjects in the control group, it is said that the study is matched. In a complementary way, when this is not done, it is said that the study is unmatched.

There are two main strategies to match cases and controls. When the aim is solely to ensure that both groups have equivalent proportions of people with the same exposure characteristics, it is said that the study is matched by frequency. In this case, cases and controls should have the same proportion of men and women, smokers and non-smokers, if matching was performed by sex and smoking habit. An alternative corresponding to a more stringent form of matching corresponds to the selection of controls guaranteeing an exact correspondence between the individuals in both groups. In this case, it is said that the study was individually matched or paired, and each case will correspond precisely to a specific control, as regards sex and smoking habit if the same variables were selected for matching. To facilitate individual pairing by age, it is customary to consider as peers the people whose ages differ by more or less 5 years.

It is important to emphasise that the difference between the case and control groups lies in the outcome, not in the exposure measure because this terminology can cause some confusion in people unfamiliar with epidemiology. Experimental studies also involve the composition of control groups for comparison with experimental groups. In such cases, however, the difference between the groups lies in the exposure factor that was controlled by the investigator. In this sense, although they are referred to by the same name, the concept of "control group" has different meanings when it comes to clinical trials or case-control studies.

Table 1.4 Association between the type of consumed food and oral cancer. Case-control study [28]

Food	Frequency	OR (95% CI)
Pork	≥ once a week	3.9 (1.2;12.0)
Soup	≥ twice a week	4.6 (1.3;16.8)
Cheese	≥ once a week	6.8 (1.7;28.0)
Bacon*fried	≥ twice a week and ≥ 4 times a week	22.2 (2.9;170.7)
Butter-margarine	≥ 7 times a week	0.1 (0.0;0.6)

Adjusted for sex, age, smoking (current status and duration), use of dental prosthesis, and adjusted for family income and other food categories included in the model

Toporcov et al. [28] carried out a compelling hospital-based control case-control study, in order to investigate the differential effect of common foods in the Brazilian diet as a risk factor for oral cancer (Table 1.4). The authors identified the association between the disease and the higher frequency of consumption of foods rich in animal or saturated fat, such as pork, soup, cheese, bacon, and fried food. On the other hand, the frequent consumption of butter or uncooked margarine, as an additive for bread and biscuits (source of vitamin A), constituted a protective factor. Characteristics such as sex, age, family income, smoking, and use of a dental prosthesis were matched for the controlled assessment of the association between food consumption and oral cancer.

As in cross-sectional studies, case-control studies have logistic advantages, such as low cost, the possibility of being developed quickly, and the simultaneous study of various risk factors. Also, they are especially useful for the study of the aetiology of rare diseases, and its application does not depend on the prospective follow-up of participants.

Difficult enrolment of an appropriate control group is one of the main problems or difficulties related to this type of study. To ensure the comparability of the groups, the techniques of restriction, stratification, matching, or adjustment in the statistical analysis are performed.

Recall bias is also a relevant problem of case-control studies. As the exposure data, in general, are collected through interviews or questionnaires, there is the risk of memory failures, in particular in the group of controls (non-patients), which generates bias. Moreover, it is important to remember that case-control studies do not allow assessing the incidence and that the measure used to estimate the association between outcome and exposure factors is the odds ratio.

1.6.6 Cohort Studies

Cohort studies are a form of longitudinal observation, whose central objective is to assess the incidence of a given disease or health condition. It includes, in general, the perspective of comparing incidence levels between groups with different status regarding exposure factors of interest. The word cohort has a military and historical origin, and it was initially applied to the units with about 300–600 soldiers, who formed the legions of the army of the former Roman Empire [29]. This analogy is useful because it suggests that a cohort consists of a group of people who present some characteristic in common. For example, in a cohort of live births, all research subjects have in common the birth period.

In cohort studies, the starting point is the exposure. The participants are healthy at the beginning and are prospectively monitored over time to record the outcome. At a given moment, the incidence of the disease is measured in the exposed and non-exposed, allowing the calculation of the relative risk. This form of organising the data implies that, in general, cohort studies are prospective. However, it is possible to consolidate data a posteriori, for the configuration of retrospective cohorts, which highlights that there are some exceptions to the general rule that cohort studies are always prospective. As an example of a retrospective cohort study in oral health, conducted in Brazil, Sousa et al. [30] followed 660 children aged 8 years old for 2 years and confirmed the effectiveness of mouthwashes with fluoride for the reduction in the incidence of caries, even in a context served by dentifrice and fluoridated water.

Cohort studies have several advantages. The quality of the data produced can be considered excellent because the risk of recall bias is small. The chronological order between exposure and outcome is recorded. Also, the same database can be used for the study of different outcomes. Cohort studies have some disadvantages such as operational difficulties including cost (higher than that of cross-sectional and case-control studies) and the need to follow up a relatively high number of research participants for a long time, even decades sometimes. In addition, cohort studies are practically not feasible for rare diseases or infrequent health conditions, since the follow-up of a considerable sample dramatically increases the operational complexity of the study. Another possible limitation to cohort studies is the fact that, as the exposure to already known factors precedes the outcomes, it is possible that this knowledge interferes in the diagnosis. Variations related to exposure factors during the follow-up, as well as changes in diagnostic criteria, can also impair the performance of cohort studies.

A cohort of 449 adults aged 50 years, in Sweden, was followed for 10 years, from 1988 to 1998, in order to describe the incidence of periodontitis and to evaluate risk factors. At the end of the follow-up, 25% of the participants, for different reasons, had abandoned the cohort. Based on this study, smoking was identified as the main risk factor for periodontitis with bone loss. The risk of the disease in exposed individuals (smokers) was 3.2 (confidence interval 95%: 2.0 to 5.1) times higher than the risk of individuals who did not smoke [31].

In the 1982 Pelotas birth cohort study, information was collected about family income at birth, adolescence and early adulthood, allowing the classification of the same according to none, one, two or three life-long episodes of poverty. When the participants completed 24 years of age, an oral health study was conducted to test the association between episodes of life-long poverty and access to dental services, smoking and the number of healthy teeth (sound + restored) [32].

Figure 1.7 shows that individuals with a higher number of episodes of life-long poverty had fewer healthy teeth, a lower proportion of dental visits in the preceding year, a lower proportion of dental visits for check-up, and a higher proportion of smokers than those who had no or few episodes of poverty in the life course.

1.7 Interventional (Experimental) Studies

Intervention or experimental studies are those in which the researcher artificially introduces an exposure in order to test a cause-effect relationship between a preventive or therapeutic procedure and the course of the disease or health condition of interest. As previously mentioned, the allocation of research subjects in the experimental or the control group is made by the exposure factors (respectively, who had and who had not the intervention) and not by the outcome (who have and who have not the disease), as in case-control studies.

1.7.1 Clinical Trials

A clinical trial is a type of intervention study, in which the starting point is the allocation of part of the participants (experimental group, test group or intervention

1

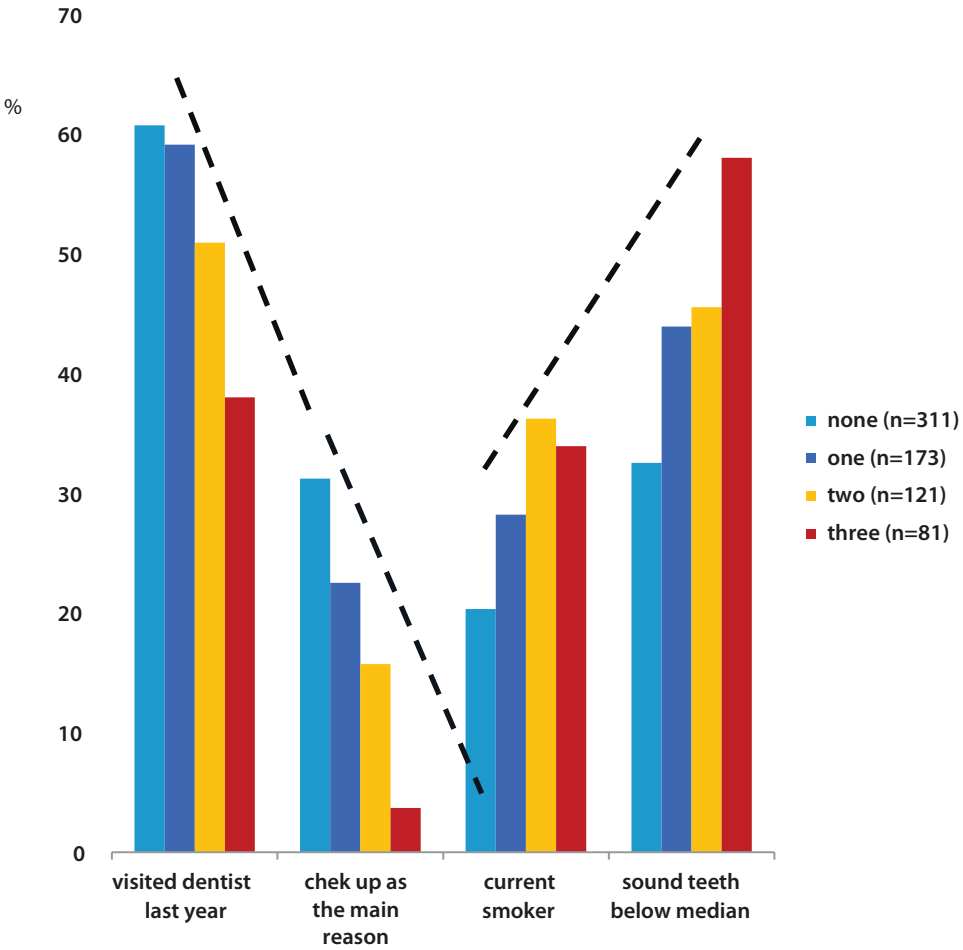


Fig. 1.7 Pattern of dental visits, smoking, and the proportion of healthy teeth at 24 years of age according to the number of episodes of poverty along life. Pelotas Birth Cohort, 1982 [32]

group) to preventive or therapeutic procedures. Another part (control group) receives the treatment as usual whose effectiveness is already known. In this sense, the primary objective of clinical trials is to evaluate endpoint treatment results, the cure of diseases, the survival of patients, or the reduction of sequelae.

In clinical trials, the researcher allocates the intervention to arm of trial (intervention vs control). When the intervention allocation criterion is at random, it is said that the study is randomised. Otherwise, the study is called a quasi-experiment. Randomised studies are termed as controlled studies because of the random allocation of individuals in the group of exposed (intervention) and non-exposed (control) groups. This allocation criterion ensures that all the characteristics that may confound the interpretation of the results are distributed equally in each group.

As an example, the work of Guimarães et al. [33] tested the effectiveness of the remineralisation of incipient caries lesions in schoolchildren, through the application of two mouthwash solutions during 14 school days, one containing 0.05% sodium fluoride (control) and another with 0.05% sodium fluoride combined with 0.12% chlorhexidine. As the groups were randomly allocated, some important population characteristics of either the test or the control group were equivalent, as shown in Table 1.5.

Table 1.5 Demographic and clinical characteristics of Group 1 (0.05% sodium fluoride) and Group 2 (0.05% sodium fluoride +0.12% chlorhexidine) at the baseline [33]

Variables	Controls (n = 85)	Test (n = 85)	p
% females	58.8%	55.3%	0.64[a]
Age in years – mean (SD)	12.96 (1.38)	13.01 (1.34)	0.88[b]
Active carious lesions: mean (SD)	6.49 (4.45)	6.55 (4.23)	0.89[b]

SD Standard deviation
[a]Chi-square test
[b]Mann-Whitney U test

Intervention studies allow the assessment of the effect in terms of the relative risk (RR) (incidence of disease in those exposed to intervention/disease incidence in non-exposed), absolute risk reduction (ARR)

Table 1.6 Synthesis of the RCT results by Feldens et al. [34]

Groups	Dental caries *n* (%)	Caries free *n* (%)	Total *n* (%)
Exposed to "Ten steps to healthy eating"	76 (53.9)	65(46.1)	141 (100.0)
No exposed	138 (69.3)	61 (30.7)	199 (100.0)

(incidence of disease in non-exposed – incidence of Disease in the exposed * 100 in %), relative risk reduction (RRR) (1 – RR * 100) and the number needed to treat (NNT) (1/ARR). The meaning of RR has already been commented. The ARR reflects the reduction in the number of cases due to intervention; the RRR expresses the same as the ARR, though regarding proportion, while the NNT means the number of people needed to be exposed to the intervention to avoid a case of the disease [37].

Feldens et al. [34] conducted an RCT with the objective of evaluating the effectiveness of home visits aimed at guiding mothers on healthy eating habits – the WHO ten steps to healthy eating: daily nutritional tips. These tips were adopted as a strategy of primary health care in Brazil and were based on guidelines proposed by the World Health Organization (WHO) for children in the first year of life. The incidence of early childhood caries and severe caries at 4 years of age was the secondary outcome of this study. The intervention group consisted of 200 mother-child pairs and the control group by 300; both constituted by mothers of children born in a public hospital in Southern Brazil. The intervention group received nutritional counselling that included the promotion of exclusive breastfeeding, gradual introduction of complementary feeding, intervals between meals, and avoiding foods with high-fat density and sugar. Table 1.6 summarises the main results of the study.

Exposure effect estimates of the intervention

Applying the formulas already described we have:

$$RR = 76/141/138/199 = 0.78;$$
$$RRR = (1 - 0.78) * 100 = 22\%$$

$$ARR = (0.69 - 0.54) * 100 = 0.15 \text{ or } 15\%;$$
$$NNT = 1/0.15 = 6.7 \sim 7$$

The results can be interpreted as follows:

- The risk of caries in the follow-up period in the intervention group was 0.78 times the risk in the group that did not receive the intervention (control), suggesting a protective effect of the intervention.
- The ten steps for healthy eating reduced the risk of caries in the follow-up period by 22% (1–0.78).
- In the group exposed to the ten steps for healthy eating, the risk of having caries was 15% lower than in the control group.
- For every seven children exposed to the intervention, one case of caries was avoided.

Moher et al. [35] recommended the use of a standardised flowchart (CONSORT guidelines), in order to encourage readers of clinical trials to understand the results, their methodology, analysis, and interpretation. Exemplifying the use of this flowchart, Fig. 1.8 shows its application to the experimental procedure of Feldens et al. [34].

Other techniques are commonly used in conducting clinical trials such as blind or masked allocation. This procedure aims to avoid errors in the measurement of the disease in clinical trials, which could be motivated, either deliberately or not, by the prior knowledge of details influencing the judgment of the observer [9, 13]. It is said that a study is blind when the observer or the observed one does not know which group (test or control) is being allocated to each participant. When they both are not aware of the allocation group, it is said that the study is double-blind. Moreover, it is said that the study is triple blind, when, in addition to the observer and the observed, the analyst of the results does not know the allocation of the groups.

Due to its methodological characteristics, the randomised clinical trial has a high probability that the intervention and control groups differ only about the intervention factor, reducing the possibility of biases. Therefore, the randomised clinical trial is considered the best type (gold standard) of study for the evaluation of health interventions. At a population level, there are arguments for the inclusion of other study designs to evaluate dental public health programmes and health policies further [36, 37]. For example, a recent Cochrane systematic review on the effectiveness of water fluoridation [38] found no evidence of the effectiveness of water fluoridation on adult dental caries. However, the Cochrane review adopted strict inclusion criteria, excluding some types of observational studies which could be limiting in evaluating public health policies such as water fluoridation [39].

Despite its undeniable advantages over other research designs to evaluate the efficacy of clinical interventions, clinical trials may be limited by ethical aspects of research involving human beings, their high costs, the need for the cooperation of participants, the impossibility of adapting the intervention to individual needs, and the possibility of modifying the results through "contamination" or "co-intervention".

"Contamination" is a technical term used to designate the event in which individuals participating in the

1

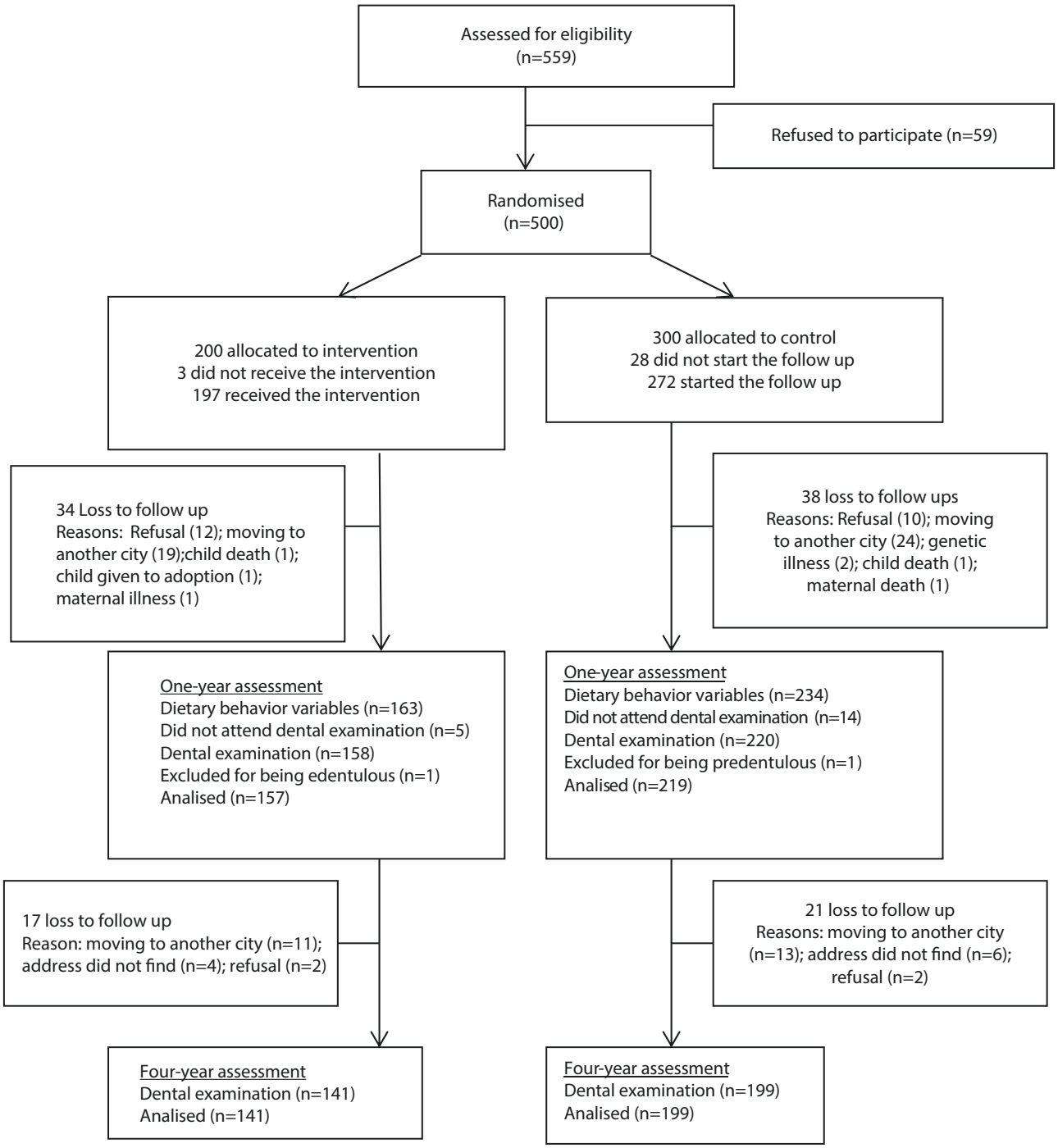


Fig. 1.8 Flowchart for RCT [35], as applied to the study by Feldens et al. [34]

control group may have access to the intervention, independently of their participation in the study. Contamination may occur when the exposure is common in the general population. If the effect of the intervention is positive, it will also benefit the part of the control group that had access to the intervention through other resources, generating an artificial decrease of the observed effect of the intervention. Additionally, there may be an artificial increase in the observed effect. When additional therapeutic procedures are performed only in the test group, then, there is a "co-intervention" [1].

As in cohort studies, the relative risk is used as the measure of effect in clinical trials. As previously mentioned, this type of research should also be considered a longitudinal and prospective study.

1.7.2 Community Intervention

In this type of experimental study, the unit of analysis and allocation for intervention is the community, a town, or a region, and not individuals. Its objective is to test the effectiveness of an intervention, which often cannot be tested through random studies.

The fluoridation of public water supply is an excellent example of this type of study. The first controlled studies began in 1945, in three towns in the state of Michigan, USA (Grand Rapids (artificially fluoridated with 1.0 ppm F), Muskegon (0.1 ppm F natural), and Aurora (1.2 ppm natural F)); in two towns of New York State (Newburgh (artificially fluoridated with 1.0 ppm F) and Kingston (0.1 ppm natural F)); and in Canada, involving the towns of Brantford (artificially fluoridated with 1.2 ppm F), Sarnia (0.1 ppm natural F), and Stratford (1.3 ppm natural F).

The second study was the first community trial that tested the effect of water fluoridation for the prevention of dental caries published in the literature [40]. The differences in age and the form of reporting the data and criteria used make it difficult to compare the three studies. Only the second study maintained control over the trial from the beginning to the end of the experiment [41].

In the Newburgh group, the decayed, missing, and filled (DMF) rates assessed either per 100 teeth or per 100 children ranked 58, 53, 48 and 41 percent less than in the Kingston group. For children aged 6–9 years, the percentage of first permanent molars free from caries was 74.0 in Newburgh and 46.7 in Kingston. For those aged 13, 14, and 16 years, DMF rates per 100 erupted first permanent molars were 1444.7, 13.5, and 3.9 lower in Newburgh than in Kingston; for second permanent molars, the corresponding differences were 51.2, 44.2, and 28.7 [40]. The positive results of these pioneering studies have stimulated the adoption of water fluoridation as a public health measure worldwide.

1.8 Internal and External Validities

Epidemiological studies should ideally have internal and external validity. The concept of internal validity refers to the possibility that the conclusions of an investigation are valid for the sample, with no systematic errors or biases. Internal validity, therefore, relates to the methodological and statistical dimensions of an epidemiological study. In order to obtain internal validity, the comparability of the groups should be ensured, the accuracy in the diagnostic technique, and the control over the factors that may hinder the interpretation.

The success of epidemiological studies relies on its inferential ability. For example, it is hoped that a survey of caries in a sample of 12-year-old schoolchildren in a given city can produce inference for the group of 12-year-old children in the city. For this aim, it is necessary that epidemiological studies have external validity along with internal validity, ensuring that the data obtained can be extrapolated to the broader universe from which their samples were selected.

External validity corresponds to the ability to generalise the results of a particular study, applying them to the population from which the sample was selected or to other populations. In addition to taking into consideration the methodological and statistical aspects, such as the criteria for calculating and selecting the sample, the possibility of inference or extrapolation should be evaluated in face of the conceptual framework on the subject that is being investigated.

Randomised clinical trials provide a good illustration of the difficulties of epidemiological studies to present both internal and external validity. As previously mentioned, these studies have strong internal validity, due to the many methodological requirements for their accomplishment. However, these studies are often subject to external validity restrictions, depending on the specific characteristics of their samples. Most of the randomised clinical trials are conducted in high-income countries, and only individuals who met various selection requirements are researched, which prevents the results from being extrapolated to the general population.

1.9 Sources of Error in Epidemiological Studies

Every study is subject to error. In epidemiological studies, errors can be systematic or random. Systematic errors occur when there is some factor that modifies the results, and this factor is more prevalent among some group of participants in the study, for instance, those affected by the disease or those exposed to some other relevant factor. When systematic errors affect the collected data, the magnitude of estimated associations can change significantly, and the researcher has no control over this process. For example, if in a case-control study the information regarding past exposures is obtained in a face-to-face interview with the cases, but through the phone with the controls, it is possible that the recollection of these exposures is more accurate in a group than in the other [45].

In turn, random errors are those that affect equally the participants, irrespective of being exposed to or affected by any other condition. Its potential effect of modifying the analysis is lower than that of systematic errors. Nevertheless, they should be avoided and duly considered in the research procedure. Random errors affect the accuracy of the studies, and overcoming it

eventually demands to increase the sample size and the commitment to improving the quality of the measurements. The most frequent systematic errors that can reduce the validity of epidemiological studies are selection bias, observation bias (information or measurement), and the existence of confounders [12].

"Bias" can be defined as any pattern in the gathering, description, analysis, interpretation, publication, or review of the data, whose potential effect is to induce different conclusions of the reality. Selection biases can occur when (i) participants are erroneously classified with respect to some characteristic of interest; (ii) participants are preferably enrolled in the study according to some characteristics; (iii) unequal allotment of individuals in the sample; (iv) loss to follow-up or non-response from participants; (v) the target population is not suitable for the research objectives; (vi) insufficient sample size for comparisons or inference of results; (vii) failure in the sample selection process; (viii) lack of equivalence of characteristics of the groups compared; (ix) generalisation of health services studies' findings to the general population; (x) non-random choice of the sample; (xi) low response or collaboration rates; (xii) loss of participants during the follow up; (xiii) lack of data quality control; and (xiv) lack of quality in the data entry [14].

In addition to selection bias, the observation bias may occur when there is a diagnosis error of a health outcome, depending on how the variables are conceptually defined or measured. The examples are the inadequate definition of "case" or "exposure", the lack of validity of the instruments for data collection, the inadequate preparation of observers, the mistaken response of people contacted, and the low diagnostic reproducibility. Finally, a confounding variable is defined as a characteristic of the observation units, when it is associated both with the exposure and with health outcomes, but it is not an intermediary path between the possible cause and effect.

The full description of updated methodological approaches to assessing and reporting bias can be seen in ▶ Chap. 33, Part III of this book.

When the estimates of the association between two factors can be attributed, entirely or partially, to a third factor not taken into consideration, this third factor is considered a confounder. There are some strategies to control confounding in epidemiological studies, such as restriction and matching, and statistical techniques, such as stratification and multivariable analysis. In case these strategies have not been applied or the study has not been planned adequately, the effect of confounding may affect the conclusion of the study.

Figure 1.9 illustrates the hypothetical relationship between an exposure variable A and an outcome E. The variables D and C are associated with the primary exposure and causally with the outcome E. The variables C and D are not steps of the causal chain between A and E. C and D fulfil the requirements to be considered (and evaluated) as confounding variables of the association between A and E. On the other hand, B is the intermediate step of the causal chain between A and E and therefore should not be considered as a confounding variable. Diagrams such as the one presented are useful for graphically synthesise formulations about causative chains based on theory.

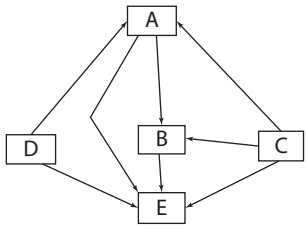


Fig. 1.9 Causal diagram illustrating hypothetically studied variables

Table 1.7 Examples of crude and adjusted effect measures (RR, PR, or OR) according to confounding type

Example	Type of confounding	Unadjusted relative risk, PR or OR	Adjusted relative risk, PR or OR
1	Positive (total)	3.5	1.0
2	Positive (partial)	3.5	2.1
3	Positive (partial)	0.3	0.7
4	Negative (total)	1,0	3.2
5	Negative (partial)	1.5	3.2
6	Negative (partial)	0.8	0.2
7	Qualitative	2.0	0.7
8	Qualitative	0.6	1.8

Adapted from Szklo and Javier Nieto [42]

Confounding can lead to overestimation of the real strength of the association and, in this case, is called positive confounding. Conversely, when the opposite occurs, confounding can lead to underestimation (negative confounding) of the effect. Another possibility is the inversion of the association, which can occur, for example, when the crude analysis indicates risk and the adjusted assessment indicate protection (or vice versa) [42]. Table 1.7 summarises examples for these different possibilities.

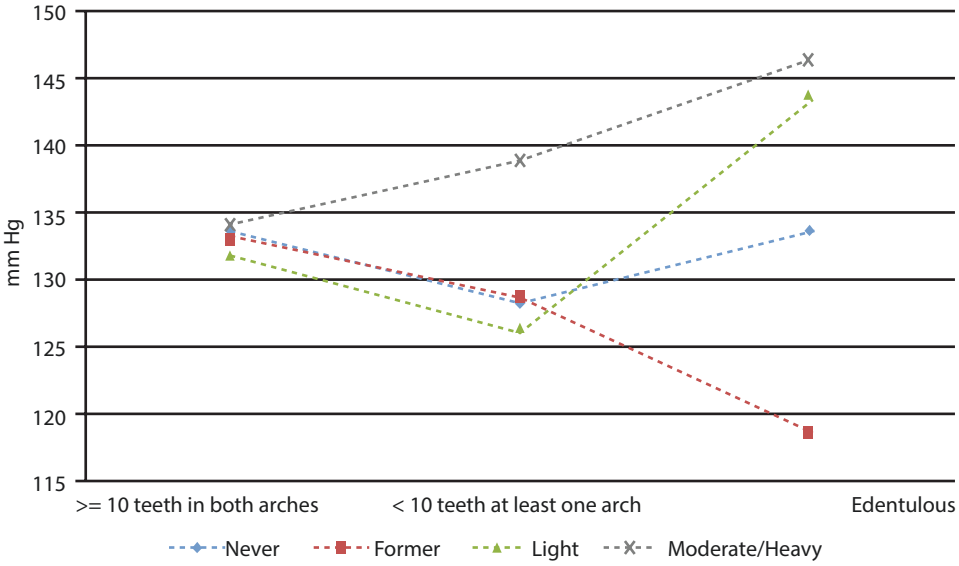


Fig. 1.10 Interaction between tooth loss and smoking in the systemic pressure of adults [43]

Interaction is the statistical term for the epidemiological concept of effect modification, an essential attribute in epidemiology. A variable is defined as an effect modifier when the measure of effect for a factor under study varies according to levels of another factor [9, 13]. For example, in a study investigating the association between tooth loss (TL) and systolic blood pressure (SBP) in adults, we attempted to identify whether tooth loss interacted with smoking and if smoking changed the effect of the association between TL and SBP [43]. Figure 1.10 shows that systolic blood pressure levels varied in different groups of the number of remaining teeth according to cigarette consumption. The conclusion is that smoking modified the effect of the association between dental losses and SBP. Moderate and heavy smokers were associated with increased SBP among edentulous, partially associated with having less than ten teeth at least in one arch and were not associated with individuals with a higher number of remaining teeth.

1.10 Final Remarks

Epidemiology is a discipline and essential practice of public health. In addition to having its own methods, epidemiology borrows methods from several areas of knowledge, such as clinical sciences, statistics, and the humanities. Epidemiology produces knowledge, instructs its application, and contributes to the monitoring of intervention programs in health. This double insertion, at one time, in the theory and practice of health is the vocation of the discipline.

On the one hand, epidemiology enables the accumulation and dissemination of scientific knowledge about the unequal and unfair aetiology and distribution of diseases and health problems in human populations. On the other hand, epidemiology is also marked by the pragmatism necessary for the elaboration of public policies and institutional interventions in the areas of health and wellbeing. Through this dual role, epidemiology embraces the mission of being at the service of improving the living and health conditions of the population.

Epidemiology has evolved from a most observational science to be a fundamental component of health and disease-oriented intervention. The discipline became a core component of health sciences and an indissociable part of the decision-making process in health policies, planning, and evaluation which lead some authors to state that there is no evidence-based health science without epidemiology [44].

References

1. Porta M. A dictionary of epidemiology. 6th ed. Oxford: Oxford University Press; 2014.
2. Snow J. On the mode of communication of cholera. London: John Churchill; 1849.
3. Townsed P, Davidnson N, Whitehead M, editors. Inequalities in health, the black report, the health divided. 2nd ed. London: Penguim books; 1988.
4. Centers for Disease Control and Prevention. Ten great public health achievements – United States, 1900–1999. MMWR Morb Mortal Wkly Rep. 1999;48(12):241–3.
5. Centers for Disease Control and Prevention, Achievements in Public Health, 1900–1999. Fluoridation of drinking water to prevent dental caries. MMWR Morb Mortal Wkly Rep. 1999;48(41):933–40.
6. Peterson B. The mentally retarded as research subjects. A research Ethics Study of the Vipeholm investigation of 1945–1955. In: Halberg M, editor. Studies in Research Ethics nr 3. Gotemborg: Centre for Research Ethics; 1995.

7. Gustafssom BE, Quensel CE, Lanke LKS, Lundqvist C, Grahnen H, Bonow BE, et al. The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed over five years. Acta Odontol Scand. 1954;11:232–364.
8. Lilienthal B, Goldsworthy NE, Sullivan HR, Cameron DA. The biology of the children of Hopewood House, Bowral, New South Wales. I. Observations on dental caries extending over five years. Med J Aust. 1953;1(25):878–81.
9. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.
10. Hill AB. The environment and disease: association or causation. Proc R Soc. 1965;58:295–300.
11. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
12. Peres MA, Barbato PR, Reis SC, Freitas CH, Antunes JL. Tooth loss in Brazil: analysis of the 2010 Brazilian Oral Health Survey. Rev Saude Publica. 2013;47(Suppl 3):78–89.
13. Hennekens CH, Buring JE, editors. Epidemiology in medicine. Boston/Toronto: Little Brown and Company; 1987.
14. Scheutz F. Basic principles and methods of oral epidemiology. In: Pine CM, editor. Community oral health. Oxford: Wright; 1997. p. 55–74.
15. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet. 2002;359(9300):57–61.
16. Armitage P, Berry G. Statistical methods in medical research. 3rd ed. Oxford: Blackwell Science; 2000.
17. Peres MA, Barros AJ, Peres KG, Araújo CL, Menezes AM. Life course dental caries determinants and predictors in children aged 12 years: a population-based birth cohort. Community Dent Oral Epidemiol. 2009;37(2):123.
18. Barros A, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003;3:21.
19. Grimes DA, Schulz KF. Descriptive studies: what they can and cannot do. Lancet. 2002;359:145–9.
20. Murray JJ, Naylor MN. Fluorides and dental caries. In: Murray JJ, editor. Prevention of oral diseases. Oxford: Oxford University Press; 1996. p. 32–67.
21. Screeby LM. Sugar availability, sugar consumption and dental caries. Community Dent Oral Epidemiol. 1982;10:1–7.
22. Morgenstern H. Ecologic studies. In: Rothman KJ, Greenland S, editors. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott Williams &Wilkins; 1998. p. 459–80.
23. Antunes JLF, Frazão P, Narvai PC, Bispo CM, Pegoretti T. Spatial analysis to identify differentials in dental needs by area-based measures. Community Dent Oral Epidemiol. 2002;30(2):133–42.
24. Gaynor PE, Kirkpatrick RC. Introduction to time-series modeling and forecasting in business and economics. New York: McGraw-Hill; 1994.
25. Antunes JLF, Biazevic MGH, de Araújo ME, Tomita NE, Chinellato LEM, Narvai PC. Trends and spatial distribution of oral cancer mortality in São Paulo, Brazil, 1980-1998. Oral Oncol. 2001;37:345–50.
26. Peres MA, Antunes JL, Boing AF, Peres KG, Bastos JL. Skin colour is associated with periodontal disease in Brazilian adults: a population-based oral health survey. J Clin Periodontol. 2007;34(3):196–201.
27. Peres KG, Luzzi L, Harford J, Peres MA. Socioeconomic gradients in toothache experience among Australian adults: A time trend analysis from 1994-2013. Community Dent Oral Epidemiol. 2018.
28. Toporcov TN, Antunes JLF, Tavares MR. Fat food habitual intake and risk of oral cancer. Oral Oncol. 2004;40:925–31.
29. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet. 2002;359:341–5.
30. Sousa ML, Marcenes W, Sheiham A. Caries reductions related to the use of fluorides: a retrospective cohort study. Int Dent J. 2002;52(5):315–20.
31. Paulander J, Wennstrom JL, Axelsson P, Lindhe J. Some risk factors for periodontal bone loss in 50-year-old individuals. A 10 year cohort study. J Clin Periodontol. 2004;31(7):489–96.
32. Peres MA, Peres KG, Thomson WM, Broadbent JM, Gigante DP, Horta BL. The influence of family income trajectories from birth to adulthood on adult oral health: findings from the 1982 pelotas birth cohort. Am J Public Health. 2011;101:730–6.
33. Guimarães ARD, Peres MA, Vieira RS, Ramos-Jorge ML, Modesto A. Effectiveness of two mouth rinses solutions in arresting caries lesions: a short-term clinical trial. Oral Health Prev Dent. 2008;6:231–8.
34. Feldens CA, Giugliani ER, Duncan BB, Drachler Mde L, Vítolo MR. Long-term effectiveness of a nutritional program in reducing early childhood caries: a randomized trial. Community Dent Oral Epidemiol. 2010;38(4):324–32.
35. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357:1191–4.
36. Victora CG, Habicht JP, Bryce J. Evidence-based public health: moving beyond randomized trials. Am J Public Health. 2004;94(3):400–5.
37. Brocklehurst PR, Baker SR, Listl S, Peres MA, Tsakos G, Rycroft-Malone J. How should we evaluate and use evidence to improve population oral health? Dent Clin North Am. 2019;63(1):145–56.
38. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, et al. Water fluoridation for the prevention of dental caries. Cochrane Database Syst Rev. 2015;18(6):CD010856.
39. Peres MA, Peres KG, Barbato PR, Höfelmann DA. Access to fluoridated water and adult dental caries: a natural experiment. J Dent Res. 2016;95(8):868–74.
40. Ast DB, Smith DJ, Wachs B, Cantwell KT. Newburg-Kinston caries-fluorine study XIV, combined clinical and roentgenographic dental finding after ten years of fluoride experience. J Am Dent Assoc. 1956;52:314–25.
41. Ast DB, Fitzerald B. Effectiveness of water fluoridation. J Am Dent Assoc. 1962;65:581–8.
42. Szklo M, Javier NF. Identifying noncausal associations: confounding. In: Szklo M, Javier Nieto F, editors. Epidemiology. Beyond the basics. 2nd ed. Sudbury, Massachusetts: Jones and Bartlett Publishers; 2007. p. 151–81.
43. Peres MA, Tsakos G, Barbato PR, Silva DA, Peres KG. Tooth loss is associated with increased blood pressure in adults-a multidisciplinary population-based study. J Clin Periodontol. 2012;39(9):824–3.
44. Jenick M. Epidemiology, evidence-based medicine, and evidence-based public health. J Epidemiol. 1997;7(4):187–97.

Further Reading

Hernan M, Robins J. Causal inference. Boca Raton: Chapman & Hall/CRC; 2019, forthcoming.

Lash TL, Fox MP, Fink AJ. Applying quantitative bias analysis to epidemiological data. New York: Springer; 2009.

Szklo M, Nieto J. Epidemiology: beyond the basics. 4th ed. Jones & Bartlett Learning: Burlington; 2019.

Vanderweele T. Explanation in causal inference. Methods for mediation and interaction. Oxford: Oxford University Press; 2015.

Global Burden of Oral Conditions

Wagner Marcenes and Eduardo Bernabé

Contents

2.1 Introduction – 24

2.2 Global and National Burden of Oral Conditions Combined – 25

2.2.1 Untreated Dental Caries – 27

2.2.2 Severe Periodontitis – 30

2.2.3 Total Tooth Loss – 32

2.3 Conclusion – 35

References – 36

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_2

2

Learning Objectives

- Readers will be able to understand the calculation and interpretation of population health metrics, namely, disability weights, years lived with disability (YLDs), and disability-Adjusted life years (DALYs).
- Readers will be able to use population health metrics to describe the global burden of oral conditions and variations by country, sex, and age.
- Readers will be able to describe the trend in the burden of oral conditions by country, sex, and age.

Summary

Nearly half of the world population suffers disability from untreated oral conditions, affecting 3.5 million people worldwide. Untreated caries in permanent teeth was the single most prevalent condition in the Global Burden of Disease (GBD) 2015 study, affecting slightly over one third of the global population. The main finding of the GBD study is that oral health has not improved during the last 25 years and a significant increase in the burden of oral conditions was observed, mainly due to aging and growing population. The widespread belief that the prevalence of oral diseases has been reduced over the past 40 years needs to be reviewed. This assumption was based on studies that analysed small data sets from few high-income countries and most included only 12 years old children. This assumption has misled public health policy makers leading to neglecting the prevention and treatment of oral health.

2.1 Introduction

Health research have been boosted in recent years by rapid technological advances that allow for the collection and management of increasingly large volumes of primary data – disaggregated to reveal the individuals and populations most in need. The Global Burden of Disease (GBD) study used all available data of sufficient quality to generate up-to-date reliable and comparable global and national estimates of the prevalence, incidence, disability weights, years lived with disability (YLDs), and disability-adjusted life years (DALYs) for oral conditions by age, sex, geography, and time.

Before delving into the global burden of oral conditions, it is necessary to clarify some terminology. Two common measures of disease frequency are prevalence and incidence. While prevalence indicates the frequency of a condition at a given point in time, incidence measures the average risk of developing the condition over a time period. The case definition of diseases has implications for the estimation of the burden of diseases – the narrower the definition of disease, the healthier the population would appear.

Beyond these conventional measures, the burden of oral conditions is presented in terms of disability weights, YLDs, and DALYs. Disability refers to any short- or long-term health loss [1]. A disability weight is a quantification of the severity of health loss associated with a unique health state on a scale from 0 to 1, when 0 corresponds with perfect health and 1 corresponds with death. For the GBD study, disability weights for health states are measured based on survey respondents representing the general public [1]. The main mode of measurement used in these surveys was a simple paired comparison question (person trade-off), in which respondents are presented with two health outcomes described briefly in lay language and then asked to imagine that both people will have these problems for the rest of their lives and answer the question: 'Who would you say is *healthier overall*, the first person or the second person?' The disability weight metric is meant to capture the severity of functional limitations and symptoms associated with each sequela in different domains of health. An oral health expert group discussed and agreed the disability definitions of health conditions [2]. The main advantage of using disability weights to measure functional limitations is that they allow standardized comparison of all health states across populations, contrary to commonly used measures of oral health-related quality of life.

YLDs are calculated as the product of prevalence (frequency) times the disability weight of the associated sequelae (severity) times the duration of symptoms [3, 4]. DALYs is estimated as the sum of the years of life lost due to premature mortality (YLLs) and years lived with disability (YLDs) [5–8]. Since death as a direct result of oral conditions is rare, it is assumed that they do not lead to YLLs. All DALY estimates for oral conditions are thus based on YLDs only. DALYs represent the health gap between the state of a population's health and a normative goal defined as the average number of years that a person at a given age can expect to live in good health, taking into account mortality and loss of functional health [7]. The assumption is for individuals to live the standard life expectancy in full health [8]. Therefore, one DALY can be interpreted as a year of 'healthy life' lost due to either premature mortality or disability and the sum of DALYs as the gap between the population's current health status and an ideal situation where the entire population lives to an advanced age, free of disease [6]. The DALYs metric is widely utilized to help decision makers and the public understand the leading causes of health burden and whether improvement occurs over time [7].

The indicators used here have been included based on their relevance to global public health; data availability and quality; and the reliability and comparability of the resulting estimates. This differs from traditional metrics used in oral epidemiology. Taken together, the indicators used in this report provide a comprehensive summary of the current status of national and global oral health and allow comparison with other fatal and non-fatal conditions.

Warning

The GBD study estimates may differ from the national statistics of countries, which may have been derived using alternative methodologies. In countries where statistical and health information systems are weak, and the underlying empirical data was not available, estimations were produced through statistical modelling.

The GBD study complies with the systematic review of literature approach proposed by the Cochrane Centre, the Strengthening the Reporting of Observational Studies (STROBE) statement and the guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). The methods of estimation have been presented in detail elsewhere (Appendix 1 in Kassebaum, Smith [9].

Important

- Nearly half of the world population suffers disability from untreated oral conditions, affecting 3.5 million people worldwide.
- Oral conditions accounted for more health loss than 35 of 39 categories of cancer.
- Health loss associated with oral conditions was comparable to those for hypertensive heart disease, schizophrenia, and all maternal conditions combined.

2.2 Global and National Burden of Oral Conditions Combined

Oral conditions remained highly prevalent in 2015 (Table 2.1). Nearly half (age-standardized prevalence: 48.0%) of the world population suffers disability from untreated oral diseases, affecting 3.5 million people

Table 2.1 Global changes 1990–2015 in the number of cases, age-standardized prevalence and incidence, DALYs and age-standardized DALYs rates due to oral conditions

	1990		2015	
Number of prevalent cases (millions)				
Untreated caries in permanent teeth	1739	(1623–1845)	2521	(2361–2680)
Untreated caries in deciduous teeth	555	(469–655)	573	(475–687)
Severe periodontitis	307	(267–357)	538	(465–626)
Total tooth loss	157	(151–164)	276	(264–288)
All oral conditions	2513	(2472–2551)	3522	(3467–3575)
Prevalence (%)				
Untreated caries in permanent teeth	34.3	(32.2–36.2)	34.1	(32.0–36.2)
Untreated caries in deciduous teeth	8.2	(6.9–9.7)	7.8	(6.4–9.3)
Severe periodontitis	7.4	(6.4–8.5)	7.4	(6.4–8.6)
Total tooth loss	4.3	(4.1–4.5)	4.1	(3.9–4.3)
All oral conditions	48.4	(47.6–49.0)	48.0	(47.3–48.7)
Number of incident cases (millions)				
Untreated caries in permanent teeth	627	(589–665)	616	(577–656)
Untreated caries in deciduous teeth	129	(98–169)	126	(94–167)
Severe periodontitis	6	(5-7)	6	(5–6.6)
Total tooth loss	3	(3-3)	3	(3-3)
All oral conditions	764	(713–820)	750	(700–808)

(continued)

Table 2.1 (continued)

	1990		2015	
DALYs (in thousands)				
Untreated caries in permanent teeth	1239	(551–2361)	1743	(777–3315)
Untreated caries in deciduous teeth	144	(62–285)	147	(63–292)
Severe periodontitis	2010	(780–4174)	3518	(1357–7247)
Total tooth loss	4334	(2898–5985)	7625	(5088–10,540)
All oral conditions	10,342	(6228–15800)	16949	(10278–26002)
Age-standardized DALY rates (per 1000 person-years)				
Untreated caries in permanent teeth	0.25	(0.11–0.47)	0.24	(0.11–0.45)
Untreated caries in deciduous teeth	0.02	(0.01–0.04)	0.02	(0.01–0.04)
Severe periodontitis	0.48	(0.19–0.99)	0.49	(0.19–1.00)
Total tooth loss	1.17	(0.79–1.62)	1.13	(0.76–1.57)
All oral conditions	2.45	(1.50–3.73)	2.41	(1.47–3.67)

worldwide. Untreated caries in permanent teeth was the single most prevalent condition in the GBD 2015 study (age-standardized prevalence: 34.1%), affecting 2.5 billion people worldwide. The age-standardized prevalence of untreated caries in deciduous teeth, severe periodontitis and total tooth loss was 7.8%, 7.4%, and 4.1%, respectively. The number of incident cases of caries in permanent and in deciduous teeth, severe periodontitis, and total tooth loss in 2015 were 616, 126, 6, and 3 million worldwide, respectively.

Age-standardized DALYs rates for oral conditions combined in 2015 were 2.4 per 1000 person-years. Total tooth loss remained the leading cause of DALYs due to oral conditions in 2015. Age-standardized DALYs rates were 1.13, 0.49, 0.24. and 0.02 per 1000 person-years for total tooth loss, severe periodontitis and untreated caries in permanent and deciduous teeth, respectively. Total tooth loss contributed 7.6 million DALYs, while severe periodontitis and untreated caries in permanent and deciduous teeth accounted for 3.5, 1.7 and 0.15 million DALYs, respectively (Table 2.1).

Table 2.1 summarizes the state of global oral health in 2015, and changes in number of cases, age-standardized prevalence and incidence, DALYs and age-standardized DALYs from 1990 to 2015 for untreated caries, severe periodontitis, total tooth loss, and all oral conditions combined for the entire globe. It also shows the progress made towards the achievement of oral health-related MDGs. Age standardisation accounts for differences in both population size and age structure [6]. Gender differences were not significant; therefore findings are presented jointly for males and females throughout this report.

While age-standardized prevalence rates in 2015 were comparable to 1990 estimates, the number of people with oral conditions increased by 40% in this period. Total DALYs due to oral conditions increased by 64% from 1990 to reach 16.9 million in 2015. Increases were mainly due to population growth and ageing (Table 2.2). This trend is likely to continue. Furthermore, there were 750 million new (incident) cases with oral conditions in 2015 (Table 2.1).

The GBD study data analysis demonstrated clearly that both the burden of oral conditions (measured by age-standardized DALYs rates) and the prevalence of oral conditions remained stable in 1990 and 2015. Overall, oral health has not improved during the last 25 years, suggesting that greater efforts and maybe a different strategy are needed if this goal is to be achieved.

Global age patterns in the prevalence and incidence of oral conditions in 2015 are shown in Fig. 2.1. The prevalence of untreated caries in deciduous teeth peaked in the 1–4 years age group globally, while that of dental caries in permanent teeth was highest in 15–19 years. Total tooth loss peaked at the age of 75–79 years, while that of severe periodontal disease peaked nearly two decades earlier. Since global age patterns have not changed appreciably since 1990, only data from 2015 is presented in this report.

DALYs and age-standardized DALY rates due to all oral conditions combined are mapped in Figs. 2.2 and 2.3, respectively. Clearly, the global distribution of

Table 2.2 Global changes (1990–2015) in number of cases and DALYs between broken down by source of variation

	Change in number of cases		Change in DALYs	
Total percent change				
Untreated caries in permanent teeth	45.0	(43.2 to 46.9)	40.6	(38.2 to 43.0)
Untreated caries in deciduous teeth	3.2	(0.78 to 5.3)	2.1	(−0.5 to 4.5)
Severe periodontitis	75.0	(72.7 to 77.3)	75.0	(72.7 to 77.4)
Total tooth loss	75.8	(75.3 to 76.3)	75.7	(75.1 to 76.3)
All oral conditions	40.2	(39.3 to 41.0)	63.9	(62.1 to 65.8)
Percent change due to population growth				
Untreated caries in permanent teeth	38.9	(38.6 to 39.2)	35.3	(33.8 to 36.9)
Untreated caries in deciduous teeth	39.6	(38.6 to 40.7)	37.6	(36.1 to 39.0)
Severe periodontitis	40.9	(40.1 to 41.9)	40.9	(40.1 to 41.8)
Total tooth loss	33.4	(33.1 to 33.7)	33.4	(33.1 to 33.7)
All oral conditions	39.1	(39.0 to 39.3)	36.4	(35.7 to 37.1)
Percent change due to population aging				
Untreated caries in permanent teeth	6.4	(4.7 to 8.2)	5.4	(3.8 to 7.1)
Untreated caries in deciduous teeth	−33.2	(−33.8 to −32.6)	−32.8	(33.4 to −32.2)
Severe periodontitis	35.4	(33.5 to 37.6)	35.2	(33.2 to 37.4)
Total tooth loss	43.2	(42.6 to 43.7)	42.8	(42.3 to 43.4)
All oral conditions	1.9	(1.5 to 2.4)	28.0	(25.9 to 30.1)
Percent change due to change in disease rate				
Untreated caries in permanent teeth	−0.4	(−1.0–0.3)	−0.1	(−0.7 to 0.5)
Untreated caries in deciduous teeth	−3.2	(−4.5 to −1.6)	−2.7	(−4.3 to −1.0)
Severe periodontitis	−1.3	(−1.97 to −0.7)	−1.1	(−1.7 to −0.4)
Total tooth loss	−0.8	(−0.94 to −0.63)	−0.5	(−0.8 to −0.3)
All oral conditions	−0.9	(−1.52 to −0.25)	−0.4	(−0.7 to −0.2)

oral diseases was uneven. According to the age-standardized DALYs rates, which take into account population size and longevity, the major burden due to oral conditions is found among countries in Latin America, Eastern Europe, and Central Asia.

2.2.1 Untreated Dental Caries

Dental caries manifests as a continuum of disease states of increasing severity and tooth destruction, ranging from sub-clinical changes to lesions with dentinal involvement [10, 11]. The initial stages of caries are asymptomatic, with symptoms starting after the carious lesion has progressed into dentine [12]. The current standard for caries detection in epidemiological surveys in most countries is the WHO criteria, which measure caries at cavitation level [13, 14]. In line with the WHO definition, the GBD study case definition of untreated caries was 'teeth with unmistakable coronal cavity at dentine level, root cavity in cementum that feels soft or leathery to probing, temporary or permanent restorations with a caries lesion' [2, 15]. The GBD study definition of disability associated with untreated symptomatic caries was 'a toothache, which causes some difficulty eating' [2, 9]. The burden of dental caries in deciduous and permanent teeth was modelled separately.

2.2.1.1 Burden of Untreated Dental Caries

In 2015, untreated caries in permanent teeth was the most prevalent condition among all 318 diseases and injuries included in the GBD study [16], an age-standardized prevalence of 34.1%, affecting 2.5 billion people worldwide. Untreated caries in deciduous teeth

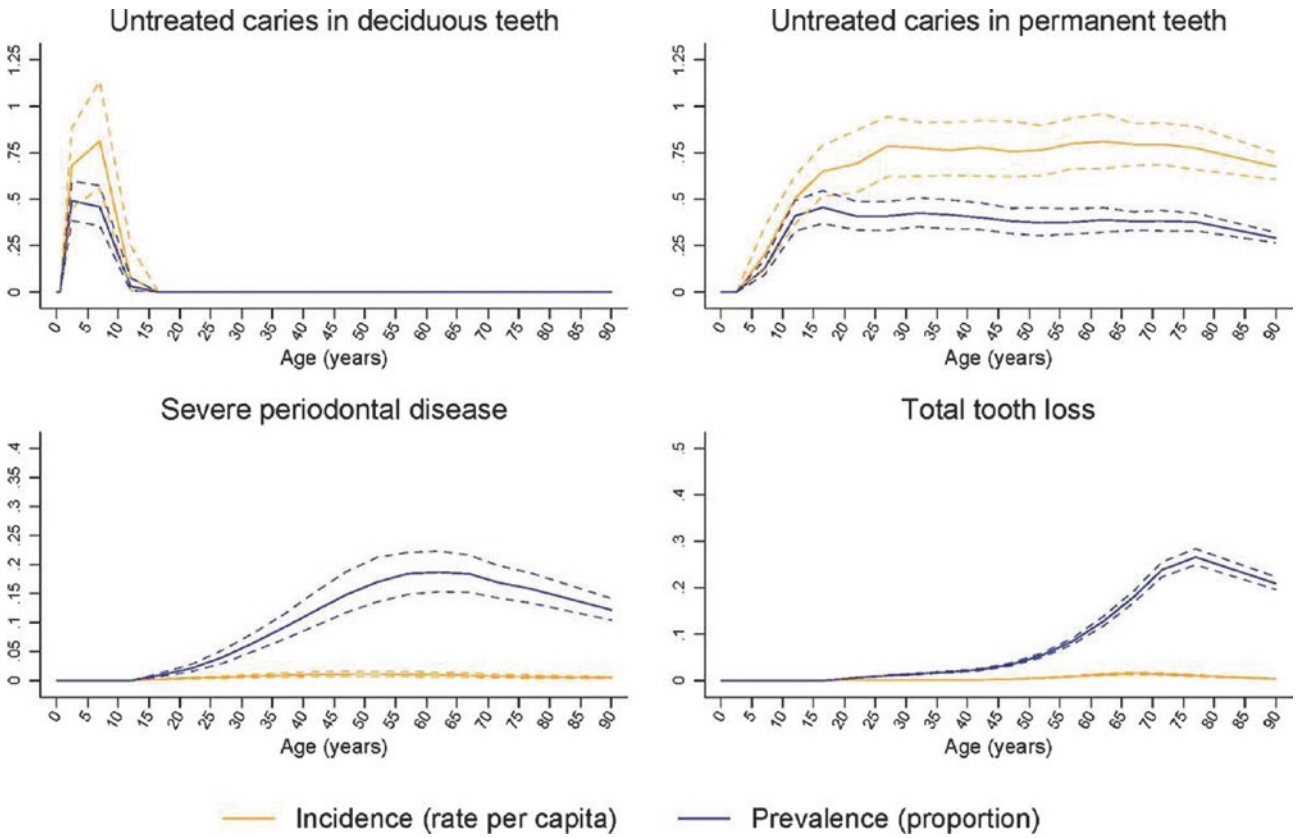


Fig. 2.1 Global prevalence and incidence rate of oral conditions in 2015 by age in 2015. The average estimate and 95% confidence intervals are shown in solid and dashes lines, respectively

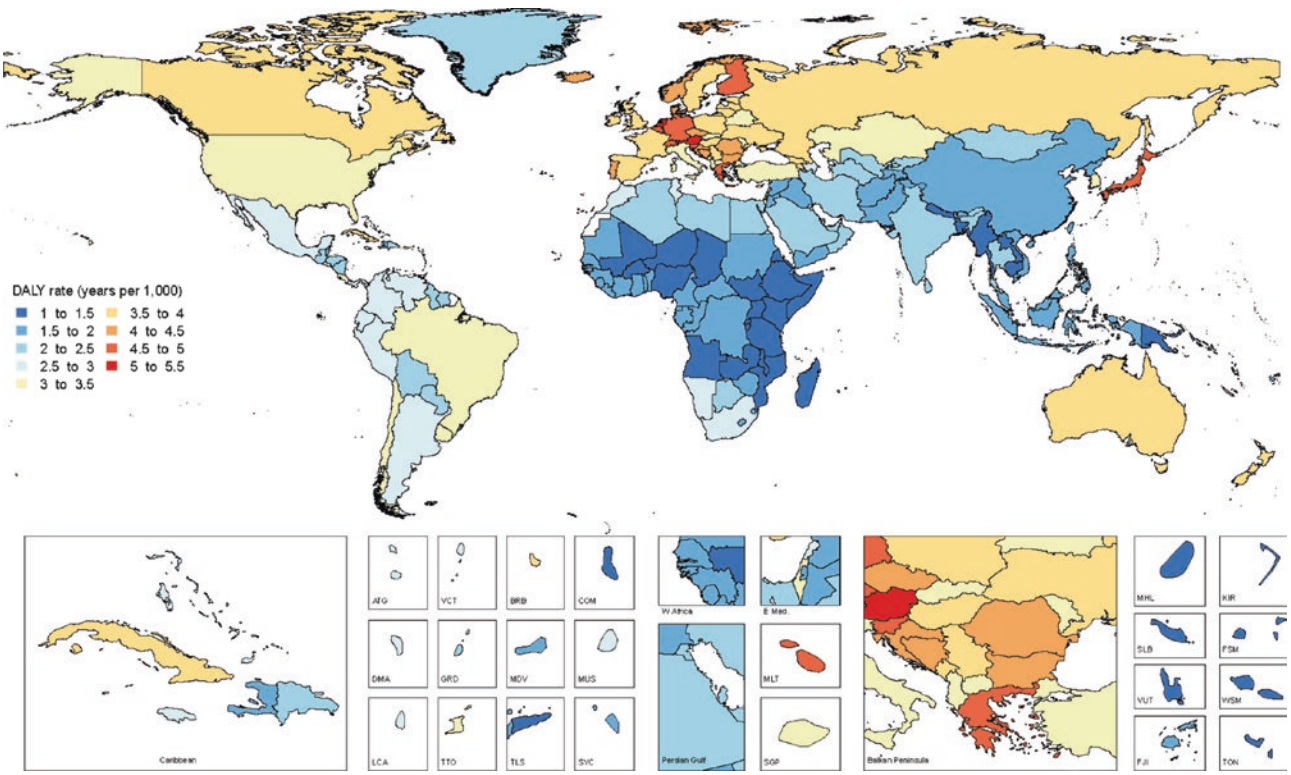


Fig. 2.2 DALYs (per 1000 population) due to all oral conditions combined (both sexes) by country in 2015

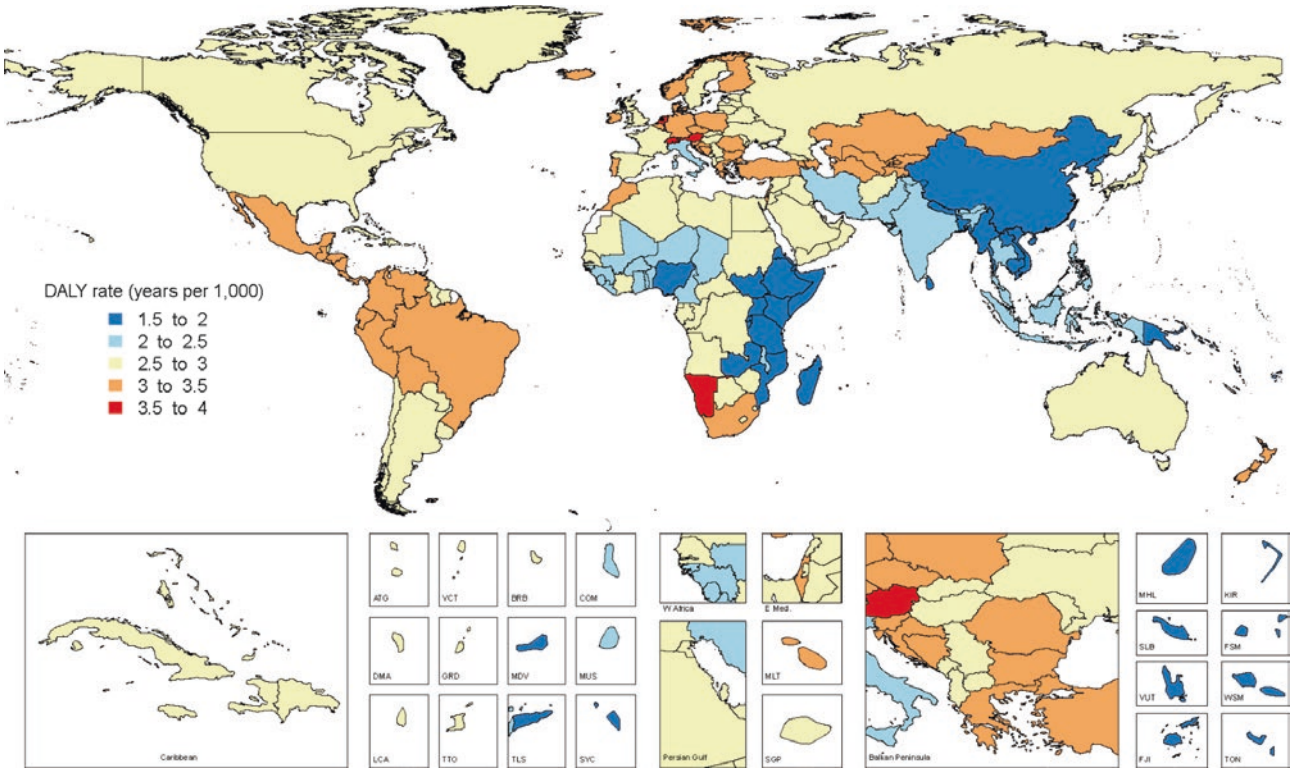


Fig. 2.3 Age-standardized DALY rates (per 1000 population) due to all oral conditions combined (both sexes) by country in 2015

was the 12th most prevalent condition [16]. The age-standardized prevalence of untreated caries in deciduous teeth was 7.8% representing 574 million people in the globe. The number of incident cases of untreated caries in deciduous and permanent teeth in 2015 were 126 and 616 million, respectively. The disability weight associated with untreated caries was closer to the lower end of the disability scale at 0.012. The age-standardized DALYs rates of untreated caries in deciduous and permanent teeth in 2015 were 2000 and 23,600 cases per 100,000 person-years, respectively. Untreated caries in deciduous and permanent teeth accounted for 147,000 and 1.7 billion DALYs in 2015, respectively.

While the age-standardized prevalence and incidence rates of untreated caries in permanent teeth for 2015 were comparable to estimates for 1990, the number of people with this condition increased by 45% in this period. DALYs due to untreated caries in permanent teeth increased by 41% from 1990 to 2015. Increases were mainly due to population growth and ageing, offsetting a static age-standardized prevalence in the same period. The incidence and total DALYs of untreated caries in deciduous teeth in 1990 and 2015 were comparable (Tables 2.1 and 2.2).

Global age patterns in the prevalence and incidence of dental caries in 2015 are shown in Fig. 2.1. It is important to note that the prevalence of untreated caries in permanent teeth was highest in the 15–19 years age group, decreasing gradually with increasing age. The burden of untreated caries seems to be shifting from children to adults. Pooled data analysis of the GBD study showed that the prevalence of dental caries increased from 26.3% at the 5–14-year age range to 41.5% at the age range of 15–49-year. Individuals are susceptible to caries throughout life [17–19], and the current assumption that the current low levels of caries in childhood will continue throughout the life course may be incorrect and may need to be monitored. It is more likely that the occurrence of caries is delayed rather than eradicated.

Considering that the filling (f/F) component of the DMFT index often accounts for a small proportion of the composite measure, these findings suggest that neither untreated caries nor caries experience are decreasing, and, instead, they are now peaking later in life. The current assumption of a remarkable decrease in dental caries experience, a 90% reduction in the number of decayed, missing and filled teeth (DMFT) for 12 year-olds between the early 1970s and the mid-1990s, in the USA and Western and Nordic European high-income countries, has misled public health policy makers and led to the neglect of the prevention and treatment of the most prevalent disease across the globe. Age-standardized prevalence and incidence rates

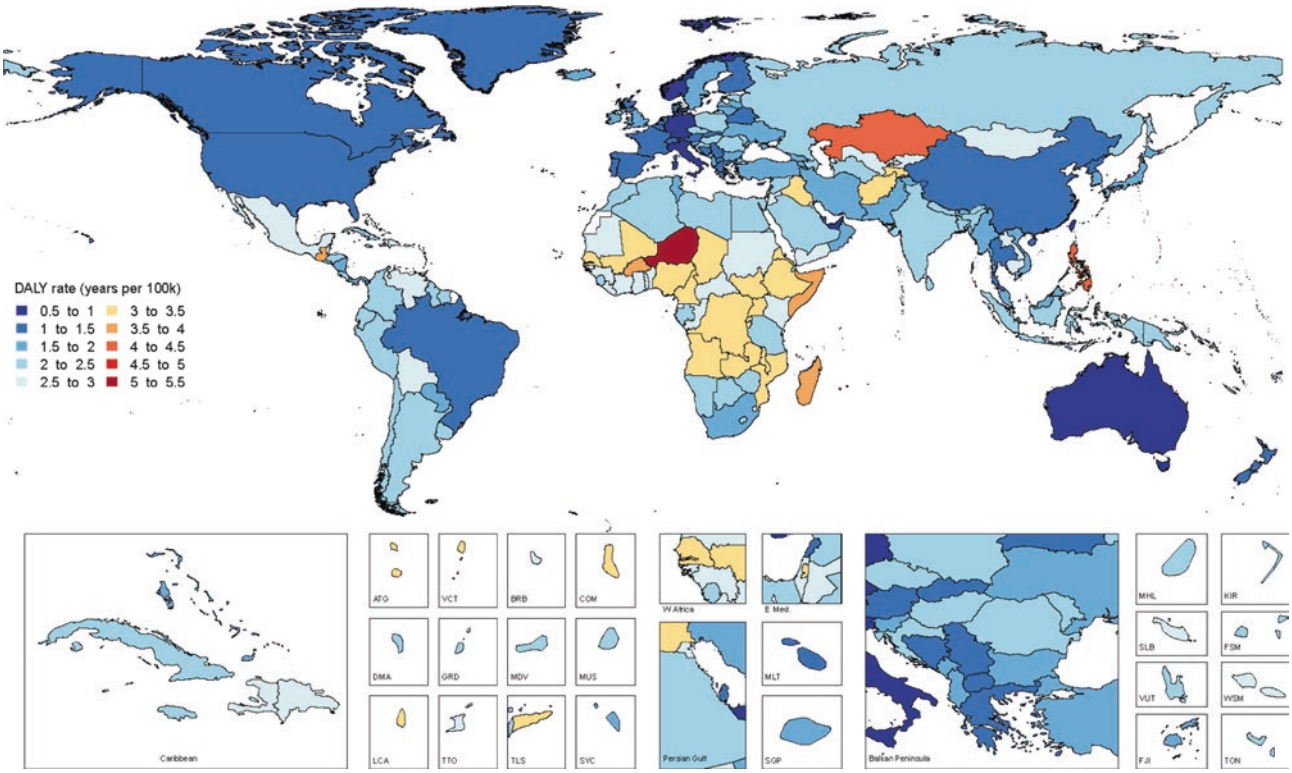


Fig. 2.4 DALYs (per 100,000 population) due to untreated caries in deciduous teeth (both sexes) by country in 2015

of untreated caries in permanent teeth remained high in 2015 and static since 1990. This finding has major implications for developing a new agenda for oral health.

DALYs and age-standardized DALY rates due to untreated dental caries are mapped in Figs. 2.4 and 2.5 for deciduous teeth and Figs. 2.6 and 2.7 for permanent teeth, respectively. According to the age-standardized DALYs rates (Fig. 2.5), the burden of untreated caries in deciduous teeth was mainly localized in Eastern Europe and North Asia, whereas the burden of untreated caries in permanent teeth was localized in Europe, North Asia, and some parts of Latin America.

2.2.2 Severe Periodontitis

Periodontitis is an inflammatory disease of the supporting structures of teeth (e.g., connective tissues and alveolar bone) which is induced by bacteria, and that results in progressive destruction of the periodontal ligament; formation of pockets around the teeth; and resorption of alveolar bone, chiefly in a horizontal direction with loosening or loss of teeth [20, 21]. The GBD study case definition of SP for detection in epidemiological surveys was as follows in order of preference, 'a CPITN score of 4, a clinical attachment loss more than 6 mm or a gingival periodontal pocket more than 5 mm', depending on which was used in the publication [2, 22]. The GBD study disability definition of SP was 'bad breath, a bad taste in the mouth, and gums that bleed a little from time to time, but this does not interfere with daily activities' [2, 9].

2.2.2.1 Burden of Severe Periodontitis

In 2015, severe periodontitis was the 14th most prevalent single condition of all 318 diseases and injuries included in the GBD study [16], with an age-standardized prevalence of 7.4%, affecting 537 million people worldwide. The number of incident cases of severe periodontitis in 2015 was 6million worldwide. The disability weight associated with severe periodontitis was closer to the lower end of the disability scale at 0.0079. Severe periodontitis accounted for 3.5 million DALYs in 2015. Age-standardized DALYs rates in 2015 were 48.6 per 100,000 person-years for severe periodontitis.

Between 1990 and 2015, the global age-standardized prevalence of severe periodontitis in the entire global population was static at 7.4%. Similarly, the global number of incident cases of severe periodontitis was static at 6 million. As for other indicators, the number of people with severe periodontitis increased from 307 million to

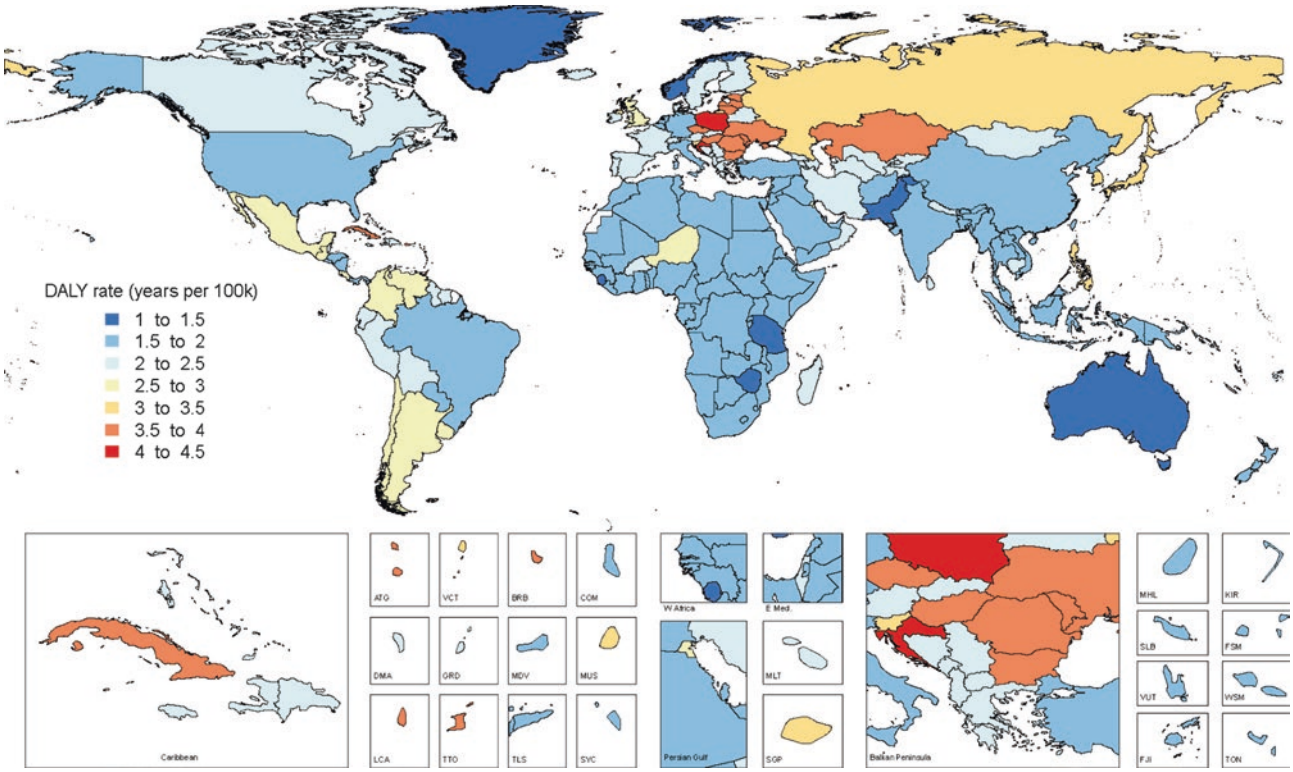


Fig. 2.5 Age-standardized DALY rate (per 100,000 population) due to untreated caries in deciduous teeth (both sexes) by country in 2015

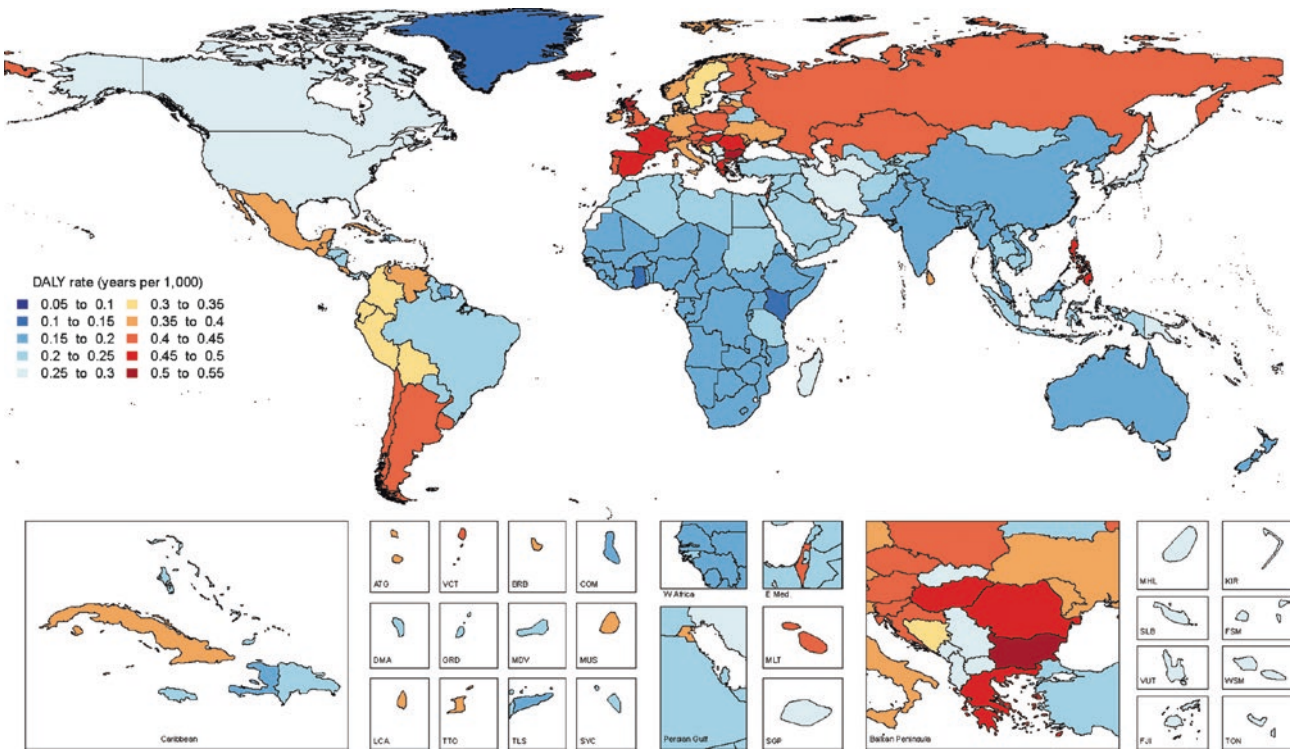


Fig. 2.6 DALYs (per 1000 population) due to untreated caries in permanent teeth (both sexes) by country in 2015

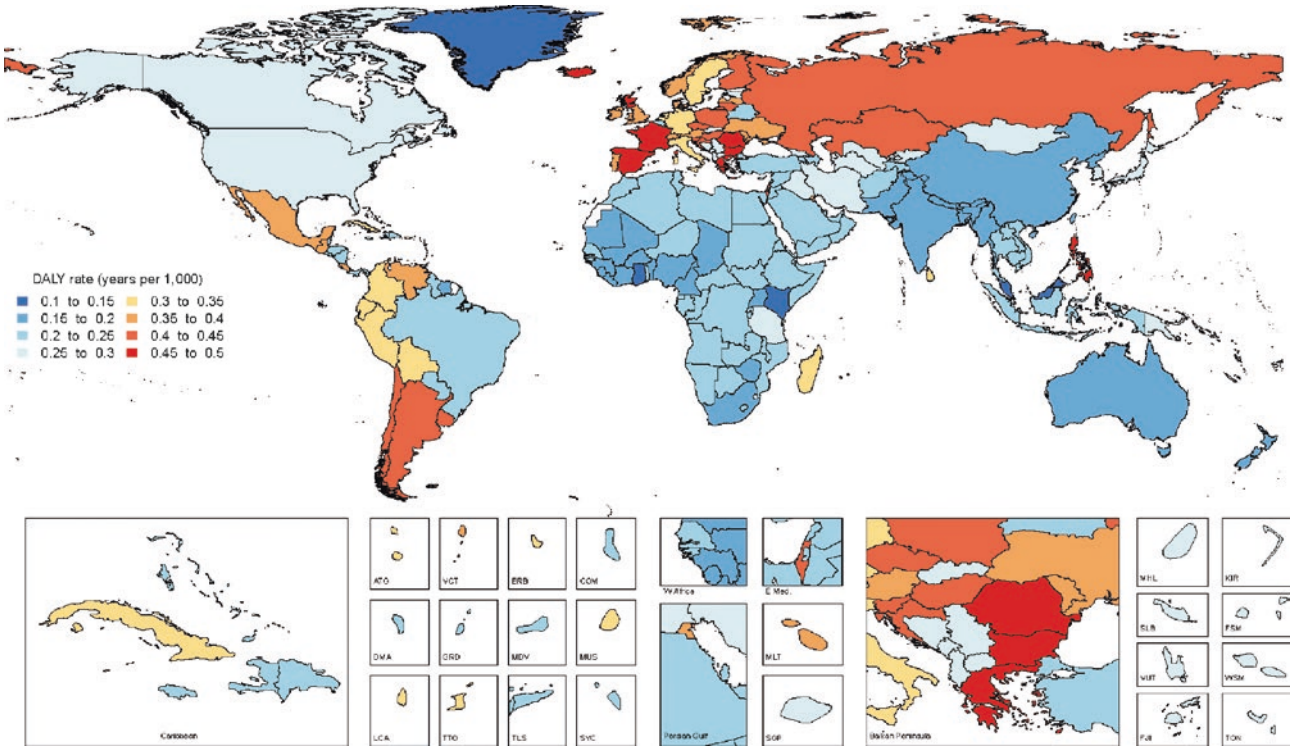


Fig. 2.7 Age-standardized DALY rates (per 1000 population) due to untreated caries in permanent teeth (both sexes) by country in 2015

538 million people worldwide, an increase of 75% from 1990 to 2015 despite age-standardized prevalence rates of this condition remaining static in this period. Total DALYs due to severe periodontitis also increased by 75% from 2 million in 1990 to 3.5 million in 2015. Increases were mainly due to population growth and ageing (Tables 2.1 and 2.2).

Global age patterns in the prevalence and incidence of severe periodontitis in 2015 are shown in Fig. 2.1. The prevalence of severe periodontitis increased gradually with age, showing a steep increase up to the age of 55 years old that was driven by a peak in incidence at between 55 and 65 years of age. The prevalence of severe periodontitis decreases at older ages, probably due to tooth loss. Although new cases of severe periodontitis developed with increasing age, incidence was low and fairly constant through the life course. These age patterns have not changed appreciably since 1990.

Trends in periodontal health are less well documented than trends in dental caries. Available evidence suggests that the prevalence of periodontal disease has declined in selected high-income countries [23–25]. There are also suggestions of a higher prevalence of periodontitis in the adult US population than previously reported [26, 27]. This coincides with changes in examination criteria from partial- to full-mouth assessment, which suggests that the change reported might have been due to changing the methodology for assessing periodontal health.

DALYs and age-standardized DALY rates due to severe periodontitis are mapped in Figs. 2.8 and 2.9, respectively. According to age-standardized DALY rates, the burden of severe periodontitis was located in parts of Africa, Latin America, and South Asia.

2.2.3 Total Tooth Loss

Tooth loss is a complex outcome that reflects both the individuals' history of dental disease and its treatment by dental services over the life course [28, 29]. Tooth loss reflects not only dental disease but also patients' and dentists' attitudes, the dentist-patient relationship, the availability and accessibility of dental services, and the prevailing philosophies of dental care [29, 30]. For these reasons, tooth loss is considered an effective marker of a population's oral health and therefore should be monitored in all countries. The definition of total tooth loss was 'complete loss of natural teeth' [2, 31]. The GBD study case definition of total tooth loss was 'having no remaining permanent natural teeth'

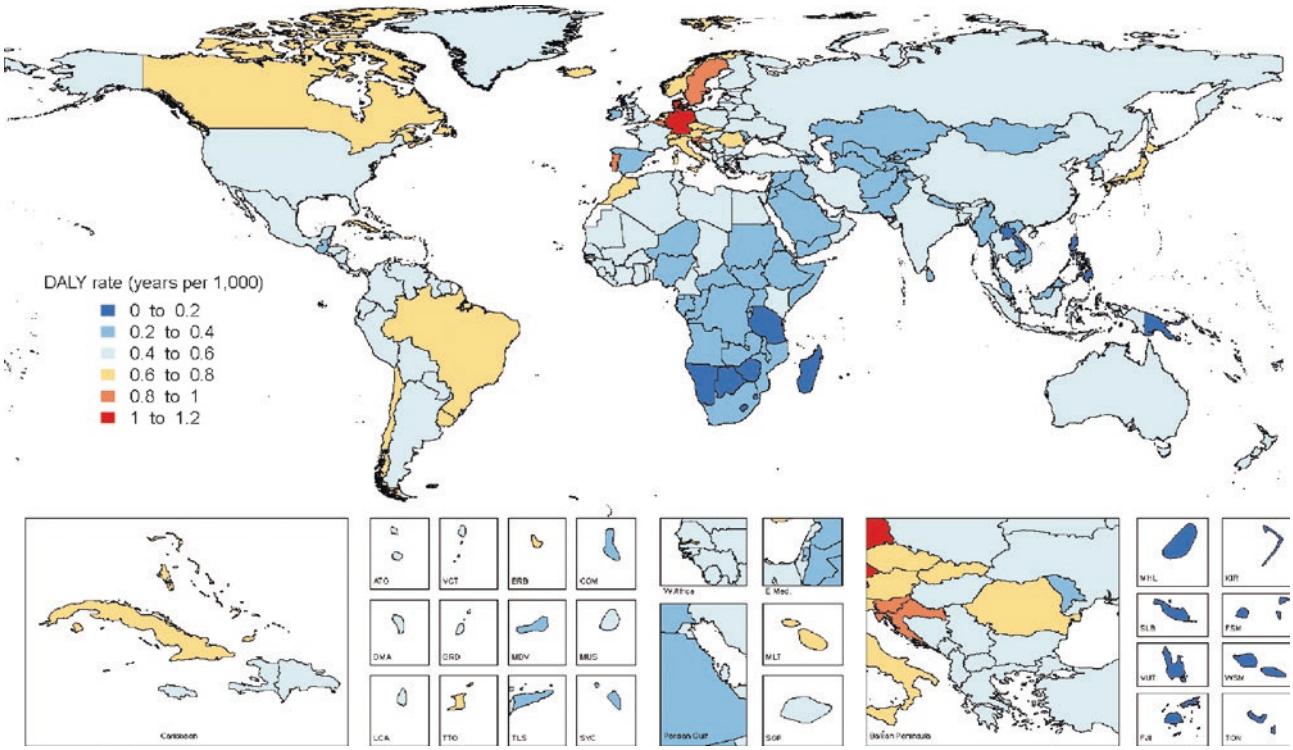


Fig. 2.8 DALYs (per 1000 population) due to severe periodontal disease (both sexes) by country in 2015

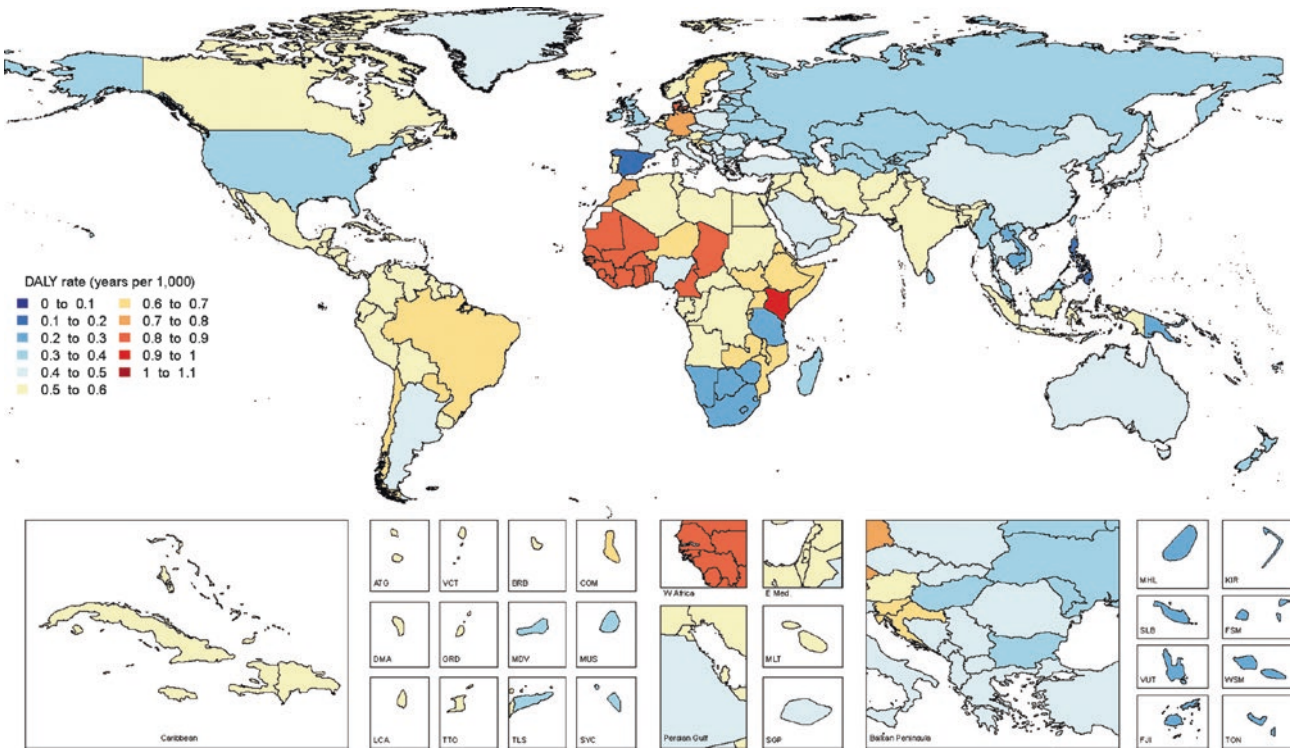


Fig. 2.9 Age-standardized DALY rates (per 1000 population) due to severe periodontal disease (both sexes) by country in 2015

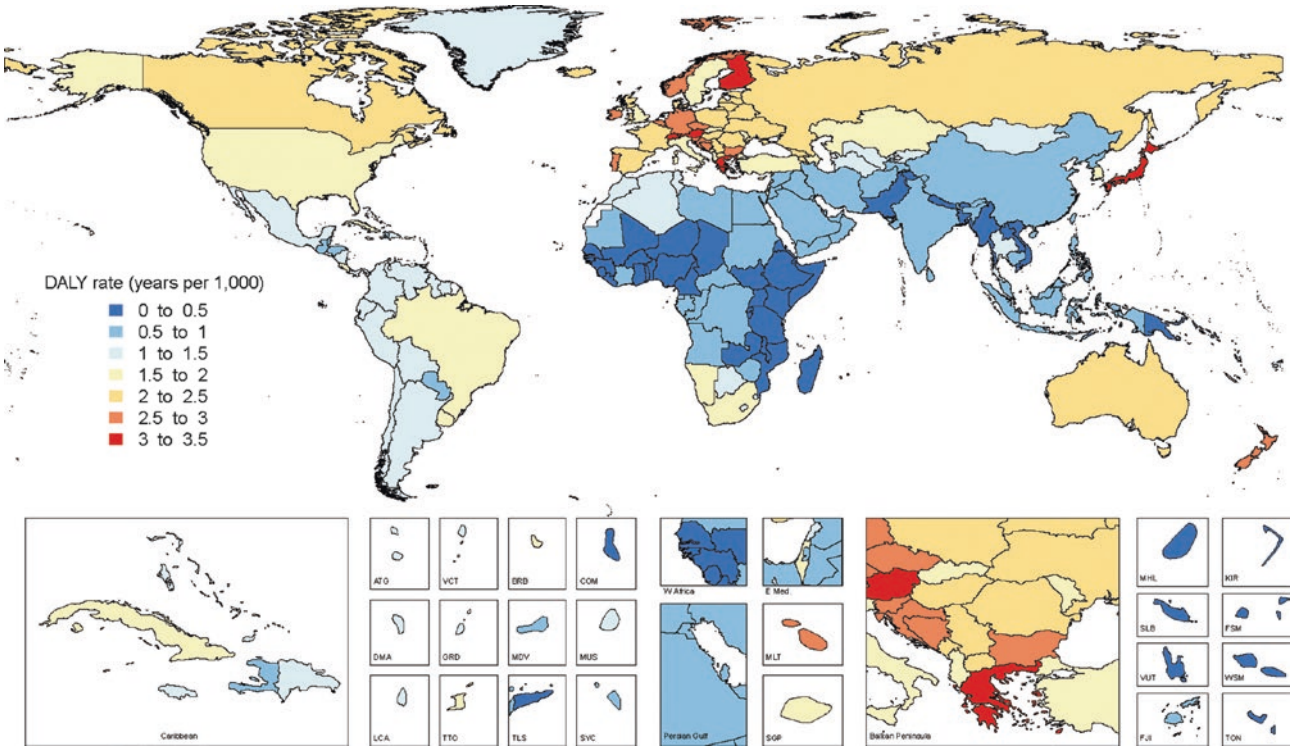


Fig. 2.10 DALYs (per 100,000 population) due to total tooth loss (both sexes) by country in 2015

with data coming from either clinical examinations or self-reports [2]. The disability definition associated with total tooth loss was 'great difficulty in eating meat, fruits, and vegetables' [9].

2.2.3.1 The Burden of Total Tooth Loss

In 2015, total tooth loss was the 28th most prevalent condition of all 318 diseases and injuries included in the GBD study [16]. The age-standardized prevalence of total tooth loss was 4.1%, affecting 276 million people worldwide. The number of incident cases of total tooth loss in 2015 was 3 million. The disability weight associated with total tooth loss was the highest of the three oral conditions assessed, at 0.073. Total tooth loss accounted for 7.6 million DALYs in 2015. Age-standardized DALYs rates in 2015 were 113 per 100,000 person-years for total tooth loss.

Between 1990 and 2015, the global age-standardized prevalence and incidence of total tooth loss in the entire population were static, and the number of people with total tooth loss increased by 76%, from 157 million to 276 million people worldwide. DALYs due to total tooth loss also increased by 76% from 4.3 million in 1990 to 7.6 million in 2015. Increases were mainly due to population growth and ageing (Tables 2.1 and 2.2).

Available evidence suggests that the prevalence of total tooth loss [32–34] has declined in selected high-income countries. As for dental caries and severe periodontitis, analysis of total tooth loss data from high-income countries showed a reduction in disease burden, while GBD study pooled data analysis of the entire world population showed no decline.

Global age patterns in the prevalence and incidence of total tooth loss in 2015 are shown in Figs. 2.1. The prevalence of total tooth loss increased gradually with ageing up to the seventh decade of life, followed by a small decrease. Although new cases developed with increasing age, incidence was low and fairly constant throughout the life course.

DALYs and age-standardized DALY rates due to total tooth loss are mapped in Figs. 2.10 and 2.11, respectively. According to age-standardized DALY rates, the highest burden of total tooth loss was found in Southern Africa, Latin America, Eastern Europe, and Australasia.

Question 1: Define disability weights, years lived with disability (YLDs), and explain how they are interpreted?

Answer 1: A disability weight is a quantification of the severity of health loss associated with a unique health state on a scale from 0 to 1, when 0 corresponds with perfect health and 1 corresponds with death. YLDs are calculated as the product of prevalence times the disability weight times duration.

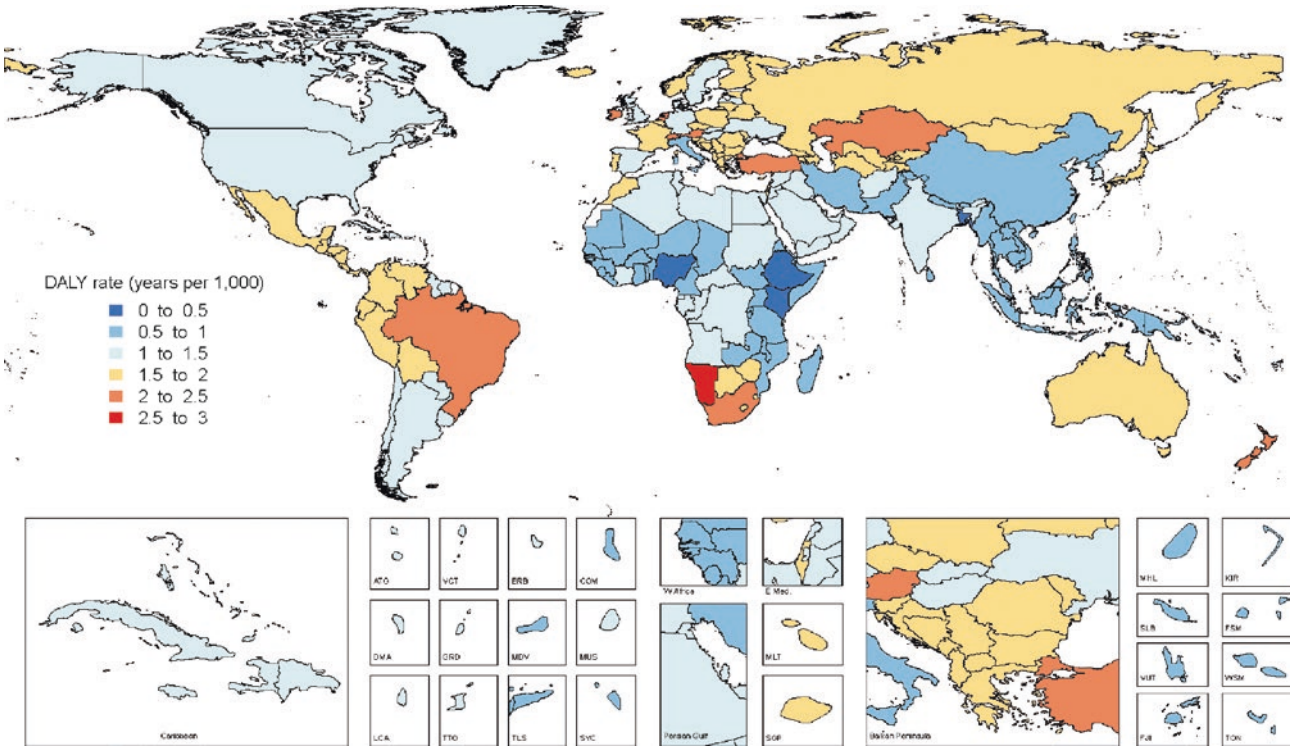


Fig. 2.11 Age-standardized DALY rates (per 100,000 population) due to total tooth loss (both sexes) by country in 2015

Question 2: What are the advantages of using health metrics widely used in the medical field?

Answer 2: The main advantage of using population health metrics is that they allow comparison of all health states across populations. Measures specifically developed to assess oral health, although important, do not allow such comparison.

Question 3: How to calculate DALYs for oral conditions and how they are interpreted?

Answer 3: Disability adjusted life years (DALYs) are calculated as the sum of years of life lost (YLLs) and years lived with disability (YLDs). Since death as a direct result of oral diseases is rare, therefore YLLs are equated to zero and DALYs estimates for oral conditions are based on YLDs only. One DALY can be interpreted as a year of 'healthy life' lost due to either premature mortality or disability and the sum of DALYs as the gap between the population's current health status and an ideal situation where the entire population lives to an advanced age, free of disease

Question 4: What are the key findings of the GBD 2015 study in relation to oral conditions?

Answer 4: The key finding of the GBD 2015 study is that oral health has not improved in the last 25 years and that oral conditions remained a major public health challenge all over the world in 2015. Untreated dental caries, severe periodontitis and total tooth loss are highly prevalent globally, posing a very serious public health challenge to policy makers.

2.3 Conclusion

Oral health remains a major population health challenge. The main finding of the GBD study is that oral health has not improved during the last 25 years, and a significant increase in the burden of oral conditions was observed, mainly due to aging and growing population. The widespread belief that the prevalence of oral diseases has been reduced over the past 40 years need to be reviewed. This assumption was based on studies that analysed small data sets from few high-income countries and most included only 12 years-old children. This

assumption has misled public health policy makers leading to neglecting the prevention and treatment of oral health. Nearly half (age-standardized prevalence: 48.0%) of the world population suffers disability from untreated oral diseases, affecting 3.5 million people worldwide. Untreated caries in permanent teeth was the single most prevalent condition in the GBD 2015 study (age-standardized prevalence: 34.1%). The age-standardized prevalence of untreated caries in deciduous teeth, severe periodontitis and total tooth loss was 7.8%, 7.4% and 4.1%, respectively. The number of new cases of caries in permanent and in deciduous teeth, severe periodontitis, and total tooth loss in 2015 were 616, 126, 6, and 3 million worldwide, respectively. The health loss associated with oral conditions was comparable to all maternal conditions combined, hypertensive heart disease, anxiety disorders, and schizophrenia, and for more YLDs than 25 of 28 categories of cancer (stomach, liver and trachea, bronchus and lung cancers ranked higher than oral conditions), cardiovascular and cerebrovascular diseases, and mental health other than depression. Greater efforts and alternative approaches to what have been attempted so far are needed to reduce the high prevalence of oral diseases and minimize their impact on individuals, families, and societies at large.

References

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2163–96.
2. Marcenes W, Kassebaum NJ, Bernabé E, Flaxman A, Naghavi M, Lopez A, et al. Global burden of oral conditions in 1990-2010: a systematic analysis. J Dent Res. 2013;92(7):592–7.
3. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2129–43.
4. Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, et al. Disability weights for the Global Burden of Disease 2013 study. Lancet Glob Health. 2015; 3(11):e712–23.
5. Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010: design, definitions, and metrics. Lancet. 2012;380(9859):2063–6.
6. GBD 2015 DALYs and HALE Collaborators. Global, regional and national disability-adjusted life years (DALYs) for 313 diseases and injuries and healthy life expectancy (HALE) for 195 countries, 1990–2015: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors (GBD) 2015 Study. Lancet. 2016;388(10053):1603–58.
7. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1859–922.
8. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380(9859):2197–223.
9. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96(4):380–7.
10. Featherstone JD. The continuum of dental caries – evidence for a dynamic disease process. Journal of dental research. 2004;83 Spec No C:C39–42.
11. Kidd EA, Fejerskov O. What constitutes dental caries? Histopathology of carious enamel and dentin related to the action of cariogenic biofilms. Journal of dental research. 2004;83 Spec No C:C35–8.
12. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet. 2007;369(9555):51–9.
13. WHO. Oral health survey: basic methods. Geneva: World Health Organization; 1997.
14. WHO. Oral health survey: basic methods. Geneva: World Health Organization; 2013.
15. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. J Dent Res. 2015;94(5):650–8.
16. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545–602.
17. Griffin SO, Griffin PM, Swann JL, Zlobin N. New coronal caries in older adults: implications for prevention. J Dent Res. 2005;84(8):715–20.
18. Thomson WM. Dental caries experience in older people over time: what can the large cohort studies tell us? Br Dent J. 2004;196(2):89–92.
19. Broadbent JM, Page LA, Thomson WM, Poulton R. Permanent dentition caries through the first half of life. Br Dent J. 2013;215(7):E12.
20. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification. J Periodontol. 2018;89(Suppl 1):S1–s8.
21. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Periodontol. 2018;89(Suppl 1):S173–s82.
22. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res. 2014;93(11):1045–53.
23. Dye BA, Tan S, Smith V, Lewis BG, Barker LK, Thornton-Evans G, et al. Trends in oral health status: United States, 1988-1994 and 1999-2004. Vital Health Stat 11. 2007;248:1–92.
24. Holtfreter B, Schützhold S, Kocher T. Is periodontitis prevalence declining? A review of the current literature. Current Oral Health Rep. 2014;1(4):251–61.

25. Wahlin A, Papias A, Jansson H, Norderyd O. Secular trends over 40 years of periodontal health and disease in individuals aged 20-80 years in Jonkoping, Sweden: repeated cross-sectional studies. J Clin Periodontol. 2018;45(9):1016–24.
26. Thornton-Evans G, Eke P, Wei L, Palmer A, Moeti R, Hutchins S, et al. Periodontitis among adults aged >/=30 years - United States, 2009-2010. MMWR Suppl. 2013;62(3):129–35.
27. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol. 2015;86(5):611–22.
28. Petersen PE, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. Bull World Health Organ. 2005;83(9):661–9.
29. Baelum V, van Palenstein HW, Hugoson A, Yee R, Fejerskov O. A global perspective on changes in the burden of caries and periodontitis: implications for dentistry. J Oral Rehabil. 2007;34(12):872–906; discussion 40
30. Fejerskov O, Escobar G, Jossing M, Baelum V. A functional natural dentition for all - and for life? The oral healthcare system needs revision. J Oral Rehabil. 2013;40(9):707–22.
31. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe tooth loss: a systematic review and meta-analysis. J Dent Res. 2014;93(7 Suppl):20S–8S.
32. Sanders AE, Slade GD, Carter KD, Stewart JF. Trends in prevalence of complete tooth loss among Australians, 1979–2002. Aust N Z J Public Health. 2004;28(6):549–54.
33. Bernabe E, Sheiham A. Tooth loss in the United Kingdom – trends in social inequalities: an age-period-and-cohort analysis. PLoS One. 2014;9(8):e104808.
34. Slade GD, Akinkugbe AA, Sanders AE. Projections of U.S. Edentulism prevalence following 5 decades of decline. J Dent Res. 2014;93(10):959–65.

Further Reading

Appendix 1: Background and GBD 2015 methods for estimating the burden of oral conditions. In, Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;s96:380–7. https://journals.sagepub.com/doi/suppl/10.1177/0022034517693566/suppl_file/DS_10.1177_0022034517693566.zip.

Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990–2010: a systematic review and meta-regression. J Dent Res. 2014a;93:1045–53.

Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe tooth loss: a systematic review and meta-analysis. J Dent Res. 2014b;93:20S–8S.

Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. J Dent Res. 2015;94:650–8.

Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96:380–7.

Marcenes W, Kassebaum NJ, Bernabé E, Flaxman A, Naghavi M, Lopez A, et al. Global burden of oral conditions in 1990–2010: a systematic analysis. J Dent Res. 2013;92:592–7.

Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, Naghavi M, Salomon JA, Shibuya K, Vos T, et al. GBD 2010: design, definitions, and metrics. Lancet. 2012;380(9859):2063–6.

Dental Caries

Karen Glazer Peres, Marco A. Peres, and Jose Leopoldo Ferreira Antunes

Contents

3.1 Introduction – 40

3.2 Measuring Dental Caries – 41
3.2.1 Indices and Instruments – 41
3.2.2 Criteria for Assessing Dental Caries – 45
3.2.3 Root Caries – 49

3.3 Analysing and Reporting Dental Caries – 49

3.4 Burden of Disease – 53

References – 55

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_3

3

Learning Aims

- Describe the major indices to measure dental caries.
- Compare the criteria for dental caries investigation among countries.
- Differentiate basic statistical techniques to analyses and interpret research data of dental caries.
- Identify and discuss the burden of dental caries worldwide.

3.1 Introduction

Dental caries is the result of a complex interaction of biological processes on the tooth surface and processes in the environment. Environment here is conceptualised as a combination of societal, contextual, and behavioural factors that influence the way caries develops in individuals and populations [1].

At tooth surface level, dental caries is the localised destruction of dental hard tissues (enamel and dentine) by acidic by-products from the bacterial fermentation of free sugars [2, 3]. When the pH in the biofilm falls below a critical level for a sustained period, this leads to progressive demineralisation and the sustained loss of calcium and phosphate from the mineral substance of the tooth. At the very early (subclinical) stages, and even once sufficient mineral is lost, and the lesion appears clinically as a white spot on the tooth surface, caries can be reversed or arrested, especially by the presence of fluoride [3, 4]. If caries progresses and leads to cavitation, the condition can cause significant pain and discomfort, and ultimately infection, and sepsis when it spreads to the dental pulp.

Dental caries is socially patterned, affecting disproportionally the most socio-economic underprivileged individuals and groups in society. It progresses steadily across the life course, achieving peaks in certain age groups. Intake of sugars is the necessary cause of dental caries, while optimal exposure to fluoride is important in limiting the disease progression, as fluoride promotes remineralisation. A regular pattern of visiting a dentist, mainly for a check-up, is also considered a determinant of dental caries [5].

Upstream social structural macro conditions (distal determinants) determine the extent, shape and nature of social networks (intermediate determinants), which provides opportunities for psychosocial mechanisms (proximal determinants), composed by social support, social influence, social engagement, person-to-person contact, and access to material resources and goods, which in turn impact on general and dental health through three different pathways: i.e. health behaviour, psychological pathways, and physiological pathways.

Macro-level social structures (ownership and control of land and business, legal and welfare structures, distribution of income and other resources) to meso-level social formation (religious institutions, family, businesses, clubs); meso-level psychosocial (social network, work control, effort/reward balance, security and autonomy, home control, work-family conflict); individual psychosocial factors – biology and behaviour which in turn will determine health outcomes. This framework can also be applied to understand dental caries in a broader perspective (Fig. 3.1).

The level of demineralisation that characterises dental caries may vary. However, caries at cavitation level is the usual criterion for caries detection in most epidemiological studies worldwide. There are many tools to assess dental caries at the population level, but the most commonly used dental caries index is the DMFT index – the sum of decayed, missing, and filled teeth due to dental caries (small letters for primary dentition/capital letters for permanent dentition) [6]. The dmft/DMFT index thus captures the cumulative experience of past and present dental caries, whether untreated (the number of decayed teeth) or treated (filled teeth or missing teeth

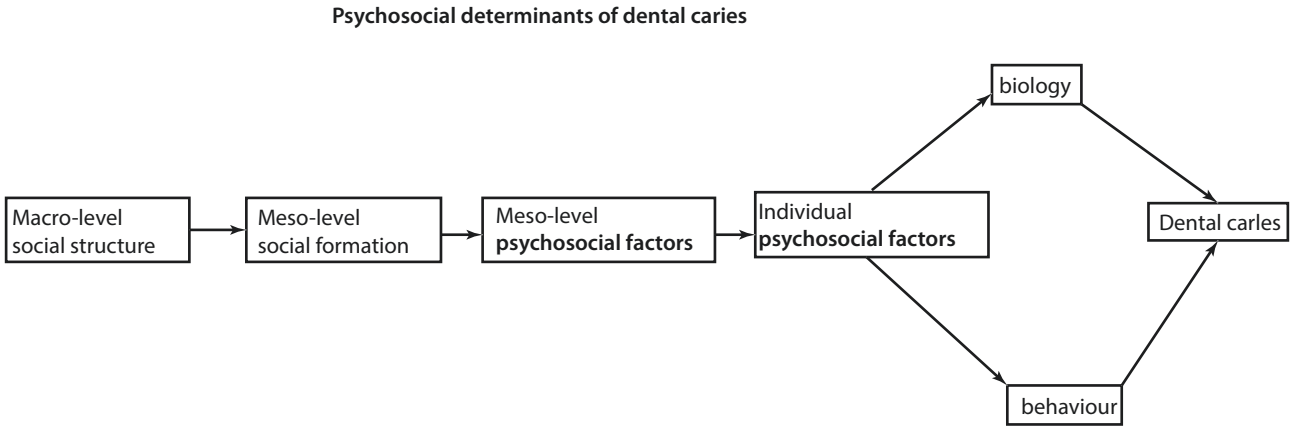


Fig. 3.1 Psychosocial determinants of dental caries. (Adapted from Martikainen et al. [53])

extracted due to caries). A particular definition is given to early childhood caries (ECC), which is a significant chronic disease and a recognised public health problem [7], that affects teeth in children aged between birth and 71 months of age. ECC is characterised by the presence of 1 or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces in any primary tooth. Severe-ECC (S-ECC) is the presence of any sign of smooth-surface caries in children younger than 3 years and the existence of one or more cavitated, missing (due to caries), or filled smooth surfaces in primary maxillary anterior teeth or a decayed, missing, or filled score of 4 (age 3), 5 (age 4), or 6 (age 5) surfaces [8].

Root caries is the caries of the cement, the decay of the root of the tooth [9]. The aetiology of root caries is similar to coronal caries, but its process of demineralisation is two-times faster than on enamel surfaces [10]. Epidemiological data on the prevalence and incidence of root caries is less frequent than for coronal caries.

In this chapter, we present the most common indices to measure dental caries at the population level, discussing the different diagnostic criteria that have been adopted in the field. We also describe the global burden of dental caries in the permanent and deciduous dentitions. Detailed explanation of the social determinants of dental caries, the role of sugar intake, the access to different sources of fluoride, and the role of dental care are comprehensively discussed in other chapters of this book.

Dental caries at the population level mostly presents skewed distributions, differing markedly, of some standard health measures in epidemiology and public health such as blood pressure, height, and weight. Consequently, this poses new challenges for dental epidemiologists and statisticians when analysing and reporting on dental caries. A review of some of the most relevant statistics dealing with dental caries is presented.

3.2 Measuring Dental Caries

In epidemiological studies, researchers want to obtain valid information about the disease under investigation, which depends on the reliability of the employed indices. It is recommended that a precise, simple, objective, reliable, able to be statistically analysed and sensitive index be used [11]. Several sets of instruments and criteria exist for assessing dental caries. They have been established since the nineteenth century when the count of the number of existing or extracted teeth was a common practice in the United States [12] and United Kingdom [13]. In the field of oral epidemiology, beyond reliability and validity, criteria definitions are essential requirements. They may vary depending on the stage of the dental caries progression the researchers wish to identify.

3.2.1 Indices and Instruments

3.2.1.1 The DMF Index

The DMF index is one of the most straightforward and commonly employed indices, which measures caries experience by quantifying the number of decayed, missing, and filled teeth due to caries in permanent teeth. The DMF index was not the first way to measure the decay, but it is undoubtedly the most known index to record caries experience, and it has persisted since the beginning of the last century. This index was introduced by Klein and Palmer [6] in 1937, and it is a quantitative expression of the cumulative caries experience in individuals or a population. Caries experience is recorded by considering three DMF-specific components: 'decayed' (aspects of disease morbidity), 'missing' (tooth mortality), and 'filled' (treatment access for restorations). Because caries rates express past and present caries experience, their values are strongly influenced by the age of the people under examination. A tooth (DMFT) or surface (DMFS) can be considered as the unit of analysis and should be included only once in one of the three categories of the index. The total DMFT of an individual can range from zero (no decayed, missing, or filled teeth) to 28 or 32 (if third molars are strictly included). DMFS index per individual can range from 0 to 128 or 148, depending on whether the third molars are included in the scoring. The equivalent index for measuring dental caries in primary dentition was described by Gruebbel [14], and it indicates the number of affected primary teeth varying from 0 to 20 (dmft), considering the complete primary dentition. The DMFS index score ranges from 0 to 88 surfaces (five per posterior tooth and four per anterior tooth) [15].

Figure 3.2 shows the DMF/dmf components. Components of the DMF index are recorded separately, with 'D' component indicating decayed, 'M' missing due to caries, and 'F' filled due to caries. Teeth are excluded if they have not erupted, are congenitally missing and supernumerary, restored for any reason other than caries, or removed for any reason than caries as, for instance, due to orthodontic treatment. Teeth with restorations with recurrent caries are counted as decayed teeth. For primary dentition, the component 'm' also includes those

Index	Unit	Dentition	Components		
dmft	Tooth	Primary	"decayed"	"missing"	"filled"
dmfs	Surface	Primary	"decayed"	"missing"	"filled"
DMFT	Tooth	Permanent	"decayed"	"missing"	"filled"
DMFS	Surface	Permanent	"decayed"	"missing"	"filled"

Fig. 3.2 Components of Klein and Palmer [6] and Gruebbel [14] indices for dental caries

primary teeth that are indicated for extraction. In some ages the distinction between teeth extracted due to caries and those that have naturally exfoliated is difficult and the category of missing teeth may be ignored (df index).

DMF/dmf indices give us a close view of the dental care utilisation by analysing the combination of 'M' and 'F' components, while the component 'D' tells us aspects of current disease morbidity. The main advantage of these indices is the opportunity of investigating the number of people affected by the disease, the number of teeth or surfaces that require treatment, the estimation of the proportion of teeth that have been treated, and the percentage of teeth that have been extracted due to decay. Statistical data allows the evaluation of programs, and the assessment of preventive measures as well as estimates of the need for funding sources, and actions in oral health. On the other hand, there are some limitations regarding DMF/dmf indices. In general, these indices give equal weight to missing, untreated decay, and restored teeth. DMFT has low discriminatory power in populations where the prevalence of the disease is low. The calculation of the component 'D' does not consider teeth or surfaces at risk (denominator) in the individual, and component 'F' is influenced by the variation in the dentist's decision to restore [16]. DMFS is influenced by the over- or underestimation of the component 'M'. In adults and the elderly, it may be biased because of the difficulty in establishing the reason for extraction. At this period of life, periodontal disease is one of the leading causes of tooth loss [17]. It is doubtful whether a researcher can determine the number of surfaces of the extracted tooth that have been affected by caries, at the time of extraction. The original proposal from 1937 indicated the assignment of three surfaces to an extracted tooth because assigning five surfaces would be overestimating the real caries experience of the teeth [18]. Researchers suggest a careful analysis of how many surfaces should be categorised as being previously decayed on an extracted tooth, particularly in research involving oral health inequalities, since this may significantly overestimate the index depending on the number of surfaces recorded as such. For longitudinal studies, the net caries increment (NCI) method seems to be more appropriate to estimate incidence, since the negative increment is subtracted from the number of positive caries increments (Fig. 3.3). Negative increment is the longitudinal progression of a surface from decay or filled to sound condition, which is known as 'true reversal' [19].

$$NCI = \frac{\sum_{i=1}^{n} \begin{array}{l}(\textit{events where surface sound at baseline but DMF in the follow–up}\\ -\textit{events where surface sound in the baseline but sound in the follow–up})\end{array}}{n}$$

Fig. 3.3 Net caries increment (NCI) formula [48]

3.2.1.2 Dental Care Index

By summing up decayed, missing, and filled teeth, the DMF index assembles information on different dimensions of the experience of caries. This index can also provide additional information by rearranging otherwise its three components. Walsh [20] proposed an original and particularly relevant way to analyse the relation among DMF components. The 'dental care index' integrates the same components of the DMF index, aiming to depict the ability of the health system to meet the demands for dental care associated with the prevalence of dental caries. For any population group, the dental care index is the ratio between the number of filled teeth or surfaces ('F' component) and the overall DMF index. Of course, a sound tooth is preferable to any form of caries experience. However, for teeth already affected by the disease, the filling is the best treatment option. Leaving untreated teeth with decay and allowing dental caries to progress until tooth extraction is needed are undesired treatment options and reflect the inability of the health system in providing appropriate dental care. Therefore, the dental care index describes how much of the overall burden of dental disease has been duly treated.

The dental care index is not a measure to be taken per person; it is an index for studies that aggregate data at the population level. It applies to comparative assessments on the effectiveness of dental care programs because it shows their greater or lesser ability to provide a suitable answer to dental treatment needs.

► Example

For instance, the care index was used to compare the coverage of dental services in children with primary dentition in German regions. The authors reported that the proportion of decayed tooth that had been filled varied from 49.3% in Bremen to 66.3% in Hessen, whereas the changing profile of the index from 2009 to 2016 varied from an increase of 40.2% in Bavaria to a decrease of 24.6% in Rhineland-Palatinate [21]. This information is certainly relevant to the planning of health services and policies related to the provision of dental care. ◄

In a scoping review, 64 studies were reported using the dental care index in surveys of child dental health. Most of these studies were conducted in the United Kingdom and Brazil; their primary objectives were to describe availability to dental care based upon socio-economic, geographical, and ethnic patterns. The authors recommended that future studies should clearly state how they defined the care index, to allow comparisons in time and across space because several studies did not, and others used alternative formulations [22].

3.2.1.3 International Caries Detection and Assessment System: ICDAS Index

From 2001 to 2005, an international group of caries researchers developed a new methodology to describe the caries experience and to allow the prospective evaluation of the incidence of the disease in different population groups. In 2007, an international caries assessment system was proposed – the International Caries Detection and Assessment System – (ICDAS). The creation of this index was an attempt to standardise data on caries prevalence given the existence of more than 30 different systems for evaluation and recording of the disease worldwide at that time. The index proposes the discrimination and recording of the earliest stages of the disease before cavitation. Therefore, the protocol of the ICDAS requires some degree of tooth cleaning before the examination, even with the recommendation of professional prophylaxis when possible. Also, the use of compressed air is necessary to reveal the earliest visual signs of caries. It implies a more detailed and prolonged examination and requires more extensive training and calibration time for the examiners [23].

The clinical stages of caries lesions were established according to the histological classification proposed by Ekstrand et al. [24], ranging from the identification of a white spot located in pits and fissures, which would require drying to be seen, to visible cavitation in dentin level. The diagnostic methodology allows visual distinctions in the case of shading, with greyish, brown, or bluish tones in dentin but with apparent enamel integrity, therefore, without a cavity. The codes of the ICDAS are composed of two digits. The former refers to the type of restorations, sealants, or crowns existing on the tooth. The second digit represents the code of caries that depends on the degree of severity of the lesion.

Studies indicate an acceptable degree of reliability (capacity to reproduce repeated measures) and validity (when the index was compared to histological examination of teeth extracted as a standard measure) [25, 26, 27]. However, the need for applying an initial cleaning protocol and the drying of the surfaces to be examined imposes logistical challenges for using this index in large-scale studies, such as national surveys. On the other hand, there is an overestimation of the caries prevalence, when considering the initial stages of the disease that the index recommends, which become a problematic comparison with studies employing a more traditional approach index, such as the DMFT index. ◘ Figure 3.4 displays the description of the ICDAS index.

3.2.1.4 Pulpal Involvement, Ulceration, Fistula, and Abscess: PUFA Index

The PUFA index was developed to help to close the existing gap in indices that focus on the description of the burden of untreated cavitated carious lesions on the tooth and its surrounding tissues [28]. It proposes a scoring of the presence of either a visible pulp, ulceration of the oral mucosa due to root fragments, a fistula, or an abscess that are related to a tooth with visible pulpal involvement because of caries. ◘ Figure 3.5 shows the codes and criteria for a PUFA index, which are assigned per tooth even if an odontogenic infection involves both the primary tooth and its permanent successor. The index represents the number of teeth that meet the PUFA/pufa diagnostic criteria and are reported separately for permanent (0–32 teeth) and primary dentition (0–20 teeth), respectively.

3.2.1.5 Caries Assessment Spectrum, and Treatment: CAST Index

This index was validated in 2014 and covers the assessment of a range of stages of carious lesions progression in enamel, dentine, and the pulp. It includes teeth with fissure sealant, filled teeth because of dental caries, teeth lost due to dental caries, and the advanced stages of a carious lesion progression in pulpal and tooth-surrounding tissue. Its codes vary from 0 to 8, and they are a combination of some of the ICDASII and PUFA index codes [29].

3.2.1.6 The British Association for the Study of Community Dentistry: BASCD

BASCD gives support for the National Health System (NHS) regarding the co-ordination of dental surveys across Great Britain [30]. The BASCD index involves visual-only examination at tooth surface level. Codes set the following conditions for surfaces: sound (S), decayed (1, 2, and 3 for arrested, dentine, and pulpal involvement, respectively), filled (4, 5, and R for filled and decayed, filled with no decay, and filling that needs replacing). Missing teeth are coded if this is due to caries (6) or orthodontic reasons (7) and for trauma (T).

3.2.1.7 Australian Research Centre for Population Oral Health, Australia: ARCPOH

ARCPOH is a research centre at the University of Adelaide in Australia, which adopts a protocol of codes following a hierarchical list of epidemiological conditions of dental caries. A code is recorded for each surface of the tooth (a total of five surfaces for posterior teeth and four surfaces for anterior teeth) as follows:

Fig. 3.4 International Caries Detection and Assessment System (ICDAS) index criteria [39]

a

First-row digits	
Code	
0	Not restored or sealed
1	Sealant, partial
2	Sealant, full
3	Tooth coloured restoration

b

4	Amalgam restoration
5	Stainless steel crown
6	Porcelain or gold or PFM crown or veneer
7	Lost or broken restoration
8	Temporary restoration
Second -row of digits	
Code	**Description**
0	Sound
1	First visual change in enamel (seen only after prolonged airdrying or restricted to within the confines of a pit or fissure)
2	Distinct visual change in enamel
3	Localized enamel breakdown (without clinical visual signs of dentinal involvement)
4	Underlying dark shadow from dentin
5	Distinct cavity with visible dentin
6	Extensive distinct cavity with visible dentin
Missing teeth	
Code	**Description**
96	Tooth surface cannot be examined: surface excluded
97	Tooth extracted because of caries (all tooth surfaces will be coded 97)
98	Tooth extracted for reasons other than caries (all tooth surfaces coded 98)
99	Unerupted (all tooth surfaces coded 99)

D (cavitation of enamel or dentinal involvement or both), R (recurrent caries), U (filled unsatisfactorily), O (filling placed for reasons other than caries), Z (fissure sealant), and S (sound). When there is a certain that two diagnoses coexist, the code that is listed higher in the hierarchy of listed codes should be recorded. On the other hand, when uncertain between two conditions, the code listed lower in the hierarchical list is recorded. Only teeth previously recorded as present, including third molars, are assessed for caries. Tooth presence is then recorded with a code for each of the 32 tooth positions, indicating if a tooth is present (P) or missing (code E –

Fig. 3.5 Codes for PUFA index [28]

Code (Permanent/primary)	Description
P/p	Pulpal involvement: the opening of the pulp chamber is visible or the coronal tooth structures have been destroyed by the carious process and only roots or root fragments are left
U/u	Ulceration due to trauma: sharp edges of a dislocated tooth with pulpal involvement or root fragment shave caused traumatic ulceration of the surrounding soft tissues, e.g., tongue or buccal mucosa
F/f	Fistula: a pus releasing sinus tract related to a tooth with pulpal involvement is present
A/a	Abscess: a pus containing swelling related to a tooth with pulpal involvement is present

missing teeth replaced by a fixed or removable prosthesis/ code M not replaced) or if it is a root fragment (code R-decayed/ code S – not decayed) or an implant (I). Teeth recorded as missing have their surfaces automatically counted as missing due to caries if participants are aged 45 years or over. Younger participants must be asked the reason for having missing teeth before being recorded in the caries index (code O – absent for reasons other than caries and replaced/code A, absent for reasons other than caries and not replaced). Root fragments are considered as all coronal surfaces decayed, and the presence of a crown placed for any reason on a permanent tooth is separately coded (C) [31]. The National Australian Oral Health surveys adopt such criteria and report estimative of dental caries prevalence and severity throughout the DMT/S indices, which include the following codes: component D (codes D + R + S), M component (codes M or E), and F (code F + U) [32].

3.2.1.8 National Health and Nutrition Examination Survey: NHANES

In 2011–2012, the Center for Disease Control and Prevention (CDC), the National Institute of Dental and Craniofacial Research (NIDCR), and the CDC/ National Center for Health Statistics (NCHS) developed an oral health component to the National Health and Nutrition Examination Surveys (NHANES) in the United States. First, the number of teeth is established for functionality; this will serve as a reference for all tooth-based assessments, including caries. Codes differentiate between primary tooth (1), a permanent tooth (2), the dental implant (3), tooth not present (4), and permanent dental root fragment (5). Caries assessment is a comprehensive dental surface-by-dental analysis. Codes characterise all tooth conditions, and specific codes are set for decayed and for filled surfaces (5 surfaces). Third molars, or wisdom teeth, are not scored for dental caries [33].

3.2.2 Criteria for Assessing Dental Caries

Final Considerations

The index originally formulated by Klein and Palmer [6], the DMFT, was based on the following dental caries criterion:

» ... Caries is recorded if frank cavitation is present or if the explorer resisted removal after the insertion into a pit or fissure with moderate to firm pressure, softness at the base of the area was identified, opacity adjacent to pit or fissures showed evidence of undermined or demineralized enamel. Also, caries was recorded in a smooth area of a buccal or lingual surface if there was a white spot as evidence of subsurface demineralisation or softness was identified by the penetration of the explorer … [6]

In addition, the category 'indicated for extraction' was recorded. It included teeth with an abscess, pulp exposure, undermining of all enamel walls, and partial or total loss of the crown.

From the 1980s, caries diagnostic criteria and other methodological indications for the epidemiological surveys of oral health were consolidated by the World Health Organization (WHO) [32] in a manual of internationally standardised technical procedures. The fifth edition of this manual was published in 2013, bringing

some changes to previous editions. In this manual, WHO recommends a visual-tactile examination for recording dental caries experience with the use of a dental mirror and a ballpoint probe [34].

Figure 3.6 presents the codes used for identification of the dental condition and the respective criteria for the diagnosis of dental caries in permanent (numbers) and primary (letters) teeth according to the WHO manual [34].

Teeth coded 6 (fissure sealant) or 7 (fixed dental prosthesis/bridge abutment, special crown, or veneer/implant) are not included in calculations of the DMFT index. In the case of the primary teeth, the calculation of the dmft index is similar, i.e. by deriving information from data codes A, B, C, and D and E (Fig. 3.6). The 5th edition of the WHO manual is innovative in providing separated oral health assessment forms for the permanent and primary dentition, as well as to record dentition status by tooth surface, allowing the calculation of the DMFS and dmfs indices. A DFT index applicable to roots can easily be calculated, as data for each tooth are collected during the examination; this index is especially relevant in older population groups.

	CODE	CRITERIA	DESCRIPTION
Primary teeth	Permanent teeth		
A	0	Sound Crown	A crown is coded as sound if it shows no evidence of treated or untreated clinical caries. The stages of caries that precede cavitation, as well as other conditions similar to the early stages of caries, are excluded because they cannot be reliably identified in most field conditions in which epidemiological surveys are conducted. Thus, a crown with the following defects, in the absence of other positive criteria, should be coded as sound: *white or chalky spots; discoloured or rough spots that are not soft, to touch with a metal CPI probe; *stained enamel pits or fissures that do not have visible cavitation or softening of the floor or walls detectable with a CPI probe; *dark, shiny, hard, pitted areas of enamel in a tooth showing signs of moderate to severe enamel fluorosis; *lesions that, on the basis of their distribution or history, or on examination, appear to be due to abrasion. *Sound root*. A root is recorded as sound when it is exposed and shows no evidence of treated or untreated clinical caries.
B	1	Carious crown	Caries is recorded as present when a lesion in a pit or fissure, or on a smooth tooth surface, has an unmistakable cavity, undermined enamel, or a detectably softened floor or wall. A tooth with a temporary filling, or one which is sealed but also decayed, should also be included in this category. In cases where the crown has been destroyed by caries and only the root is left, the caries is judged to have originated in the crown and is therefore scored as crown caries only. The CPI probe should be used to confirm visual evidence of caries on the tooth surface(s). Where any doubt exists, caries should not be recorded as present. *Carious root*. Caries is recorded as present when a lesion feels soft or leathery on probing with the CPI probe. If the carious lesion on the root does not involve the crown, it should be recorded as root caries. For single carious lesions affecting both the crown and the root, the likely site of origin of the lesion should be recorded as the decayed site. When it is not possible to identify the site of origin, both the crown and the root should be coded as decayed. In general, root caries is not recorded for children and in youth or young adults.

Fig. 3.6 WHO criteria for recording dental caries. 5th edition [34]

C	2	Filled crown, with caries	Crown is considered filled, with decay, when it has one or more permanent restorations and one or more areas that are decayed. No distinction is made between primary and secondary caries and the same code applies regardless of whether the carious lesions are in contact with the restoration(s). *Filled root, with caries.* A root is considered filled, with caries, when it has one or more permanent restorations and one or more areas that are decayed. No distinction is made between primary and secondary caries. In the case of restorations involving both the crown and the root, identification of the site of origin is more difficult. For any restoration involving both the crown and the root with secondary caries, the most likely site of the primary carious lesion is recorded as filled, with decay. When it is not possible to identify the site of origin of the primary carious lesion, both the crown and the root should be coded as filled, with caries.
D	3	Filled crown, with no caries	A crown is considered filled, without caries, when one or more permanent restorations are present and there is no caries anywhere on the crown. A tooth that has been crowned because of previous decay is recorded in this category. A tooth that has been crowned for reasons other than caries by means of a fixed dental prosthesis abutment is coded 7 (G). *Filled root, with no caries.* A root is considered filled, without caries, when one or more permanent restorations are present and there is no caries anywhere on the root. In the case of fillings involving both the crown and the root, identification of the site of origin is more difficult. For any restoration involving both the crown and the root, the most likely site of the primary carious lesion is recorded as filled. When it is not possible to identify the site of origin, both the crown and the root should be coded as filled.
E	4	Missing tooth due to caries	This code is used for permanent or primary teeth that have been extracted because of caries and are recorded under coronal status. For missing primary teeth, this score should be used only if the subject is at an age when normal exfoliation would not be a sufficient explanation for absence. *Note*: *The root status of a tooth that has been scored as missing because of caries should be coded "7" or "9".*
_	5	Permanent tooth missing due to any other reason.	This code is used for permanent teeth deemed to be absent congenitally, or extracted for orthodontic reasons or because of periodontal disease, trauma, etc. As for code 4, two entries of code 5 can be linked by a line in cases of fully edentulous arches. *Note*: *The root status of a tooth scored 5 should be coded "7" or "9"* .

Fig. 3.6 (continued)

F	6	Fissure sealant	This code is used for teeth in which a fissure sealant has been placed on the occlusal surface, in pits or for teeth in which the occlusal fissure has been enlarged with a rounded or "flame-shaped" bur, and a composite material placed. If a tooth with a sealant has caries, it should be coded as 1 or B.
G	7	Fixed dental prosthesis abutment, special crown or veneer	This code is used under coronal status to indicate that a tooth forms part of a fixed bridge abutment. This code can also be used for crowns placed for reasons other than caries and for veneers or laminates covering the labial surface of a tooth, on which there is no evidence of caries or a restoration. *Note*: *Missing teeth replaced by fixed partial denture pontics are coded 4 or 5 under coronal status, while root status is scored 9.* *Implant*. This code is used under root status to indicate that an implant has been placed as an abutment.
_	8	Unerupted tooth (crown).	This classification is restricted to permanent teeth and used only for a tooth space with an unerupted permanent tooth but no primary tooth. Teeth scored as unerupted are excluded from all calculations concerning dental caries. This category does not include congenitally missing teeth, or teeth lost as a result of trauma etc. For differential diagnosis between missing and unerupted teeth, see code 5. *Unexposed root*. This code indicates that the root surface is not exposed; there is no gingival recession beyond the cement-enamel junction (CEJ).
_	9	Not recorded	This code is used for an erupted permanent tooth that cannot be examined for any reason such as orthodontic bands, severe hypoplasia, etc. This code is used under root status to indicate either that the tooth has been extracted or that calculus is present to such an extent that root examination is not possible.

Fig. 3.6 (continued)

The WHO recommends some ages and age groups for dental examination in nationwide surveys of the general population. Children aged 5–6 years are usually attending primary school, which may logistically be easier for the investigation of primary dentition. At 12 years of age, children have the full permanent dentition except for third molars, and they are usually attending primary schools. This age is considered the global indicator age group for international comparisons and surveillance of dental caries trends. Measurements of caries in adolescents are recommended to be collected at 15 years of age or between 15 and 19 years. The 35–44 age group is a standard age group for surveillance of oral health conditions in adults, and 65–74 years age group represents the older population. This last group is particularly relevant for the investigation of root caries and an estimation of other oral diseases and conditions [34].

Changes in dental caries assessment criteria have significantly impacted on the prevalence and severity of dental caries. A study investigated dental caries, in the 12–13-year-old children who attended a single school, over 45 years, and a marked reduction in the rates of dental caries was identified. However, part of this reduction was attributed to changes from more sensitive criteria [6] to another less sensitive to caries lesions [34]. The first recommends the use of an exploratory probe for tactile detection of lesions on dental surfaces, while the WHO suggests the use of an exploratory probe only for the removal of food debris or dental plaque. The adoption of more conservative criteria was implied in the significant drop in the DMFT from 6.3 to 3.0 in 1997 [34]. Changes in the WHO criteria overtime did not affect the results [35].

The use of the ICDAS index needs specific approaches depending on the surfaces and the position of the tooth under investigation, and whether there are

restorations, or a sealant associated with the caries lesion. For example, prolonged drying (5 seconds) is recommended to investigate initial evidence of caries in pit and fissures of smooth surfaces. On the other hand, visual change in enamel must be viewed wet as well as other advanced phases of the caries process. ICDAS criteria also recommend the gentle use across a tooth surface of a WHO/CPI/PSR probe to confirm the presence of a cavity apparently confined to the enamel or in the dentin. As with most indices, if any doubt exists, the more conservative score should be adopted [23].

BASCD diagnostic criteria are centred on the use of a ball-ended CPI probe for the diagnosis of a dentine lesion. The probe includes a built-in lamp for ease of visual inspection and makes these criteria compatible with the requirements proposed by the WHO's latest manual [33] and therefore allows comparison with other studies [4]. The BASCD standards for clinical examinations have been applied since 1996/1997 national surveys until the more recent surveys in 2017 [36].

Criteria proposed by the ARCPOH at the University of Adelaide consider a surface as decayed when there is cavitation of enamel or dentinal involvement or both throughout visual criteria. A discontinuity of the enamel surface caused by the loss of tooth substance due to caries must be present. Lesions with the dentinal involvement are coded as decayed even if the lesion has hardened and appears to have 'arrested', which is not always applied in the WHO criteria [34]. Decayed dentine is judged for pits and fissures when opacity or discolouration indicates caries of dentine that is undermining adjacent enamel. For smooth surfaces on buccal and lingual surfaces, the surface is etched, or there is a white spot and dentine seems to be involved as indicated by discolouration of dentine. For proximal surfaces, the same criteria as smooth surfaces are applied, or if the marginal ridge shows darkening/shadowing as evidence of caries of the dentine, or after using transillumination in anterior teeth, it is possible to see a shadow in a calculus-free and stain-free proximal surface [31].

3.2.3 Root Caries

The increase in life expectancy over the past few decades has been impacted by the relevance of the investigation on root caries, mainly in middle- and high-income countries [37]. Caries lesions in dental roots are progressive lesions that appear below the cementoenamel junction, not including the adjacent enamel. Both tissues, dentin, and cementum, can be involved, usually presenting discoloured, softened, and imprecise lesions because of the much lower mineral content and a significant organic component when compared with coronal enamel and dentine. In general, criteria for the epidemiological diagnosis of root caries lesions are based on location, colour, texture, cavitation, and contour of the involved surfaces [38]. Carious lesions in root surfaces may be associated with yellow/orange, light brown, or black surfaces. The use of a probe is required to detect textural changes in the diagnosis by dragging the probe across the root surface and gently feeling for any softness. Most of the criteria indicate root decay when there is a lesion that is soft to exploration using the periodontal probe. Attention is necessary to differentiate sound cementum from carious cementum based on tactile sense, since normal cementum is softer than enamel, and frequently will yield to pressure from the tip of a probe. In some incipient lesions, the carious area of the root surface may merely be discoloured without cavitation, but the area will be soft to probing. Some criteria [31] recommend that arrested lesions that are hardened on probing should be coded as sound, even if the lesion is cavitated, while in others [34] there is no clear distinction regarding arrested lesions. Figure 3.7 shows the WHO's criteria for root caries.

The ICDAS index has been used to assess coronal and root surface caries. It is recommended that researchers base the conclusion of root caries activity on the discoloured area on the root surface. These characteristics include texture (smooth, rough), appearance (shiny or glossy, matte, or non-glossy), and perception on gentle probing (soft, leathery, hard). Nonvital teeth are scored the same as vital teeth. A score will be assigned per root surface [23]. According to the revised criteria for this index [39], the codes are as follows (Fig. 3.8):

3.3 Analysing and Reporting Dental Caries

The growth in knowledge related to the distribution of dental caries, and the recognition of the decline of its experience and severity in certain age groups, and areas of the globe, underlines the importance of a more analytical approach to this disease. This is particularly relevant when the phenomenon well known as 'polarization' plays a significant role, not only for the outline of the epidemiological profile of the disease but also for the ways of analysing the results. People who have less access to social benefits and health resources are more likely to have a more concentrated higher level of the disease. An interesting way of describing and explaining caries rates was proposed by Douglas Bratthall [40], which took into account the polarized, non-normal nature of caries' distribution in some populations. The Significant Caries Index (SiC) proposed by Brathall corresponds to the calculation of the mean DMF for the group of one-third of the examined participants who presented the highest values of the DMF index (Fig. 3.9).

CODE	CRITERIA	DESCRIPTION
0	Sound root	A root is recorded as sound when it is exposed and shows no evidence of treated or untreated clinical caries.
1	Carious root	Caries is recorded as present when a lesion feels soft or leathery on probing with the CPI probe. If the carious lesion on the root does not involve the crown, it should be recorded as root caries. For single carious lesions affecting both the crown and the root, the likely site of origin of the lesion should be recorded as the decayed site. When it is not possible to identify the site of origin, both the crown and the root should be coded as decayed.
2	Filled root, with caries	A root is considered filled, with caries, when it has one or more permanent restorations and one or more areas that are decayed. No distinction is made between primary and secondary caries. In the case of restorations involving both the crown and the root, identification of the site of origin is more difficult. For any restoration involving both the crown and the root with secondary caries, the most likely site of the primary carious lesion is recorded as filled, with decay. When it is not possible to identify the site of origin of the primary carious lesion, both the crown and the root should be coded as filled, with caries.
3	Filled root, with no caries	A root is considered filled, without caries, when one or more permanent restorations are present and there is no caries anywhere on the root. In the case of fillings involving both the crown and the root, identification of the site of origin is more difficult. For any restoration involving both the crown and the root, the most likely site of the primary carious lesion is recorded as filled. When it is not possible to identify the site of origin, both the crown and the root should be coded as filled.
4	Missing tooth due to caries	The root status of a tooth that has been scored as missing because of caries should be coded "7" or "9"
5	Permanent tooth missing due to any other reason.	The root status of a tooth scored 5 should be coded "7" or "9"
7	Fixed dental prosthesis	Missing teeth replaced by fixed partial denture pontics are coded 4 or 5 under coronal status, while root status is scored 9.
8	Unexposed root	This code indicates that the root surface is not exposed; there is no gingival recession beyond the cement-enamel junction (CEJ).
9	Not recorded	This code is used to indicate either that the tooth has been extracted or that calculus is present to such an extent that root examination is not possible.

Fig. 3.7 WHO criteria for root caries [34]

Another proposal to measure and illustrate inequalities in the distribution of dental caries is the use of the Gini coefficient [41]. The Gini coefficient is a measure of statistical dispersion aimed at representing income or wealth distribution. This index is the most commonly used measurement of inequality and corresponds to a standardised average of all possible differences to be calculated in a sample, among the values of any measures for which there is an interest in scaling the inequality. The Gini coefficient of zero expresses perfect equality, where all values are the same (for example, where everyone has the same income). A Gini coefficient of 1 (or 100%) expresses maximal inequality among values. The Gini index can also be calculated using graphical

Fig. 3.8 ICDAS criteria for root surfaces [39]

Code	Description
E	Excluded root surfaces (no gingival recession)
0	Sound (no caries or restoration)
1	Non-cavitated carious root surface—soft or leathery
2	Non-cavitated carious root surface—hard and glossy
3	Cavitated (greater than 0.5mm in depth) carious root surface—soft or leathery
4	Cavitated (greater than 0.5mm in depth) carious root surface—hard and glossy
6	Extensive cavity: an extensive cavity involves at least half of a tooth surface and possibly reaching the pulp
7	Filled root with no caries
9	Used for the following conditions
97	Tooth extracted because of caries (tooth surfaces will be coded 97)
98	Tooth extracted for reasons other than caries (all tooth surfaces coded 98)
99	Unerupted (tooth surfaces coded 99)

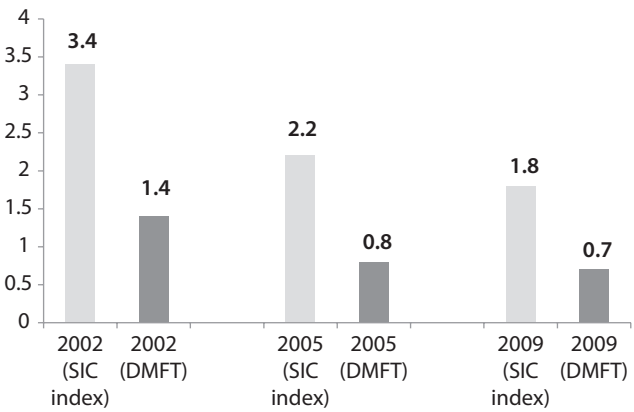


Fig. 3.9 SiC index for dental caries. Trends in dental caries from 2002 to 2009 among schoolchildren in Florianopolis, southern Brazil

resources, involving the plotting of Lorenz curves (Fig. 3.10). The curve is a graph showing the bottom x% of the population and what percentage (y%) of the total income they have. The percentage of population is plotted on the x-axis and the percentage of income on the y-axis [42].

Either the Gini coefficient or the Lorenz curve can be applied to calculate and represent the inequality in the caries experience. For instance, the experience of caries in a population can be represented by the value of the DMF index. In this case, a minimum value of the Gini coefficient equal to zero corresponds to the absence of inequality in the caries experience; that is, all individuals have the same DMF. The higher the value of the GINI coefficient, the greater is the inequality in the caries distribution, which means a reduced proportion of people who display very high values of DMF, while the majority is free of caries.

► Example

The graph below displays inequality in the dental caries distribution using the Lorenz curve (Fig. 3.11). While the DMFT index of 12-year-old school children in the Southern Brazilian city of Chapeco declined from 3.4 in 1996 to 1.9 in 2002, the Gini coefficient of caries distribution increased from 0.49 to 0.58 in the same period, which represents the increase in dental caries experience concentration from 49% to 58%. ◄

Ordinary least-square models, traditionally used to analyse DMF indices, assume that outcomes are normally distributed and might yield a biased estimate if that assumption is violated. Over the past 20 years, the decline in children's caries experience [43] has generated DMFT or DMFS indices in young people, frequently to a low count, or with an excess number of zeros (i.e. caries-free children). To overcome the characteristics of overdispersion and the high numbers of caries-free children (DMF = 0), standard statistical approaches of parametric models for non-normally distributed data, including Poisson, negative binomial, and zero-inflated models, have been recommended.

The number of events occurring in a fixed period follows the Poisson distribution. The classic example of such distribution is a count. Count data assumes only non-negative integer values, small-valued observations (e.g., counts of 0, 1, 2), starting at some value, and frequencies that decrease very rapidly, and the mean of observations is approximately equal to their variance and less frequently higher values (illustrated by a long right tail). As the mean count increases, the skewness diminishes, and the distribution becomes approximately normal. For non-negative count outcomes, a model with Poisson distribution is much more appropriate than an ordinary least-square linear model [44]. For example, DMFT between 300 participants in a survey shows the most frequent scores between one and three values, a rapid decrease from DMFT = 4 and DMFT = zero as a common response (Fig. 3.12).

The negative binomial distribution is an alternative to the Poisson model and is especially useful for count data whose sample variance exceeds the sample mean (i.e. data with overdispersion). The negative binomial distribution appears to look like the Poisson but with a longer, fatter tail, to the extent that the variance exceeds the mean. If the observed outcome is suspected of having variance higher than the mean, the negative binomial distribution of the outcome is more appropriate than either the Poisson or normal distributions [45].

Zero-inflated Poisson and other zero-inflated models have been developed to cope with zero-inflated outcome data with overdispersion (negative binomial) or without Poisson distribution. Distribution for inflated zeros data is a combination of distributions already known. The observed data are distributed discreetly in the set of positive integers, but that includes many observations at the extreme equal to zero. The probability distribution is a mixture between a discrete distribution and a degenerate distribution of 0. The proposed model is part of the class of inflated models where a mass of points equal to zero exceeds what is allowed by the Poisson model. Zero-inflated models pre-suppose that some zeros are observed due to some specific structure in the data. These models assume that some zeros occur by a binary distribution that generates structural zeros and others follow a Poisson process that generates counts that may be zero. Figure 3.13 shows a zero-inflated Poisson model with the zero observations split into two processes at work – due to their structural or sampling origin. The first one determines if the individual is even eligible for a non-zero response, and it is known as 'structural zeros' (black portion of the zero bar). The other part determines the count of the response for eligible individuals, known as 'sampling zeros' (the grey portion of the zero bar). Sampling zeros are due to the usual Poisson (or negative binomial) distribution, which assumes that those zero

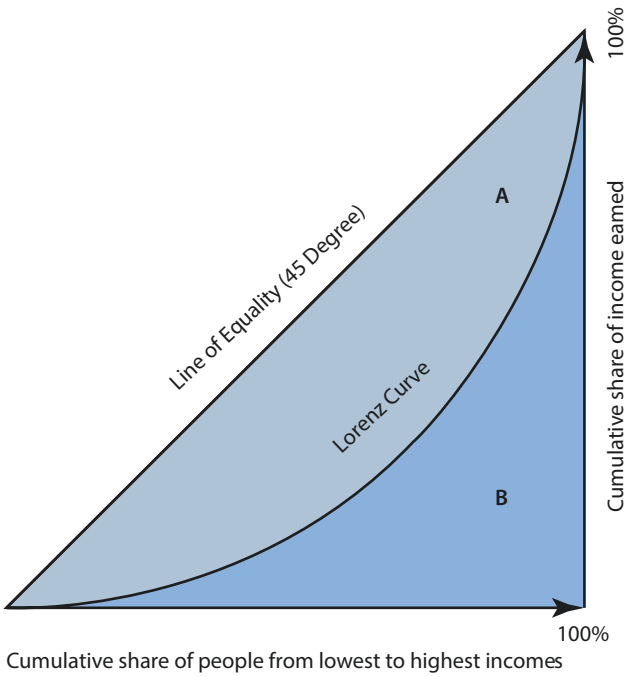


Fig. 3.10 Lorenz curve

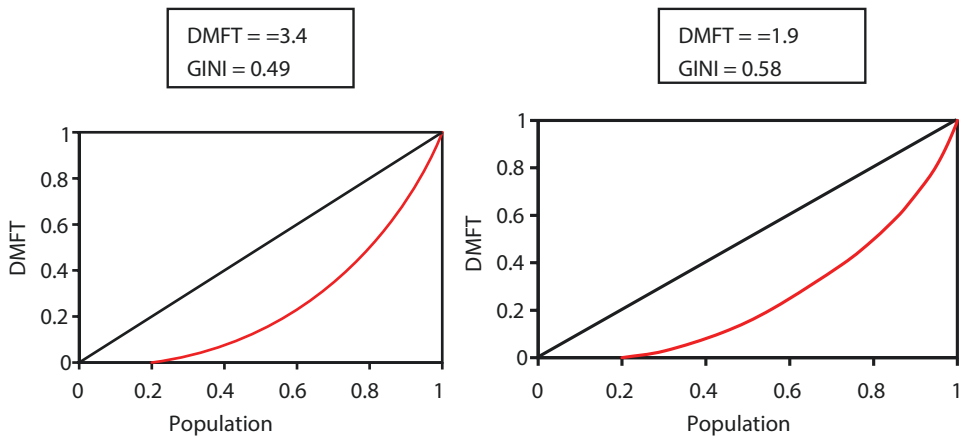


Fig. 3.11 Lorenz curves for caries distribution in 1996 and 2002. Chapeco, SC, Brazil

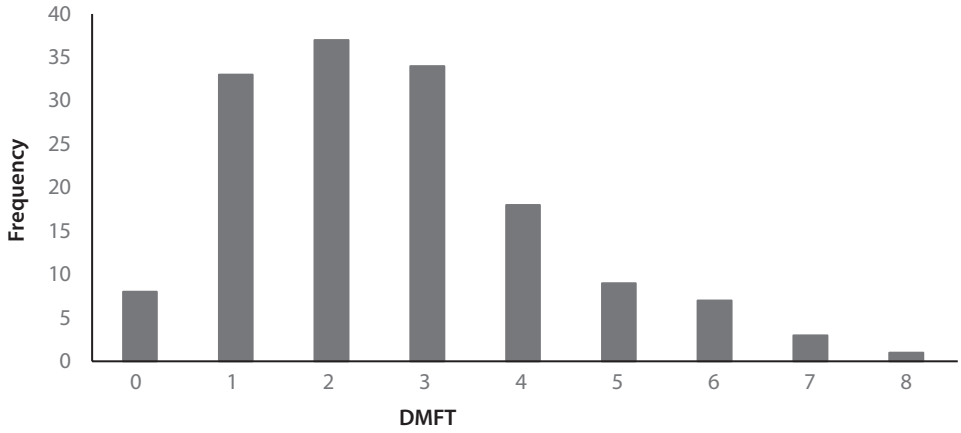


Fig. 3.12 Poisson distribution for DMFT (n = 300) – hypothetical data

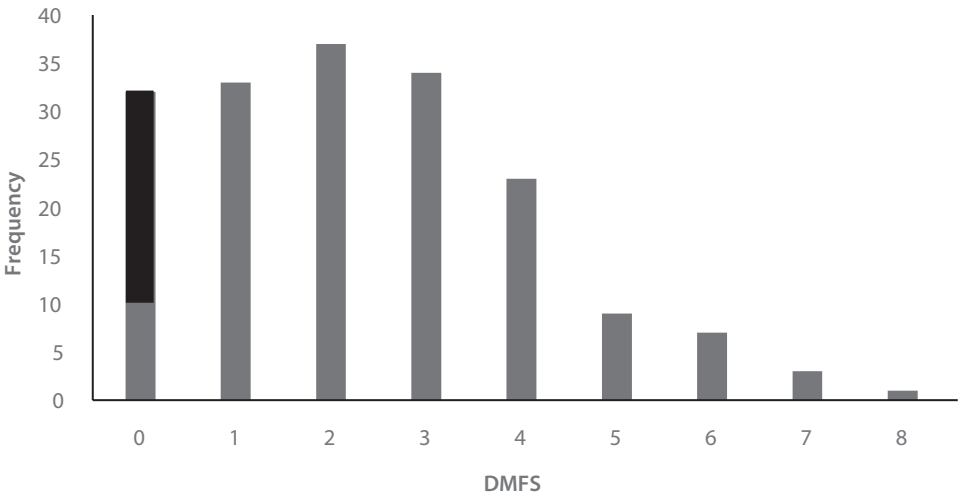


Fig. 3.13 Zero-inflated Poisson distribution for DMFS index (hypothetical data)

observations happened by chance. Two separate regression models are estimated in the zero-inflated approach. One is a logistic model that models the probability of being eligible for a non-zero count, and the other models the size of that count. They provide separate coefficients, and predictors can have significantly different effects on the two processes [46].

3.4 Burden of Disease

Caries at cavitation level is the usual criterion for caries detection in most of the epidemiological studies worldwide. The most commonly used dental caries index is the dmft – the sum of teeth that are decayed, missing due to caries, and filled due to caries for primary dentition – and the congener DMFT index for permanent dentition. Therefore, from here on, when referring to dental caries, cavitated lesions which are a cumulative measure of past and present disease are meant, even if teeth have been treated (restored). This distinction is necessary, given that it is a consensus that lifetime prevalence of dental caries has declined in the last four decades, mainly in high-income countries, with the most significant decline accounting for 90% of 12-year-old children. This result is less consensual in low-income countries [47]. The very few existing population-based cohort studies, with oral health sub-studies including clinical examination, revealed that the dental caries increment is relatively stable throughout life [48, 49]. A systematic review of longitudinal studies of the dental caries increment, with at least 3 years of follow-up, was conducted to identify the pattern of caries' progression in children and adolescents. Pooled caries progression could not be performed for deciduous dentition. For the permanent dentition, the caries incidence rate was 0.11 per person-year at risk, an increment in DMFS of 0.43 per year of follow-up or an increment in DMF of 0.18 per year of follow-up [50].

Therefore, it seems reasonable to assess the burden of untreated dental caries in primary dentition from the time when the first teeth emerged to adolescence; similarly, for permanent dentition, the current assessment starts at the age of 5 or 6 years until late in life.

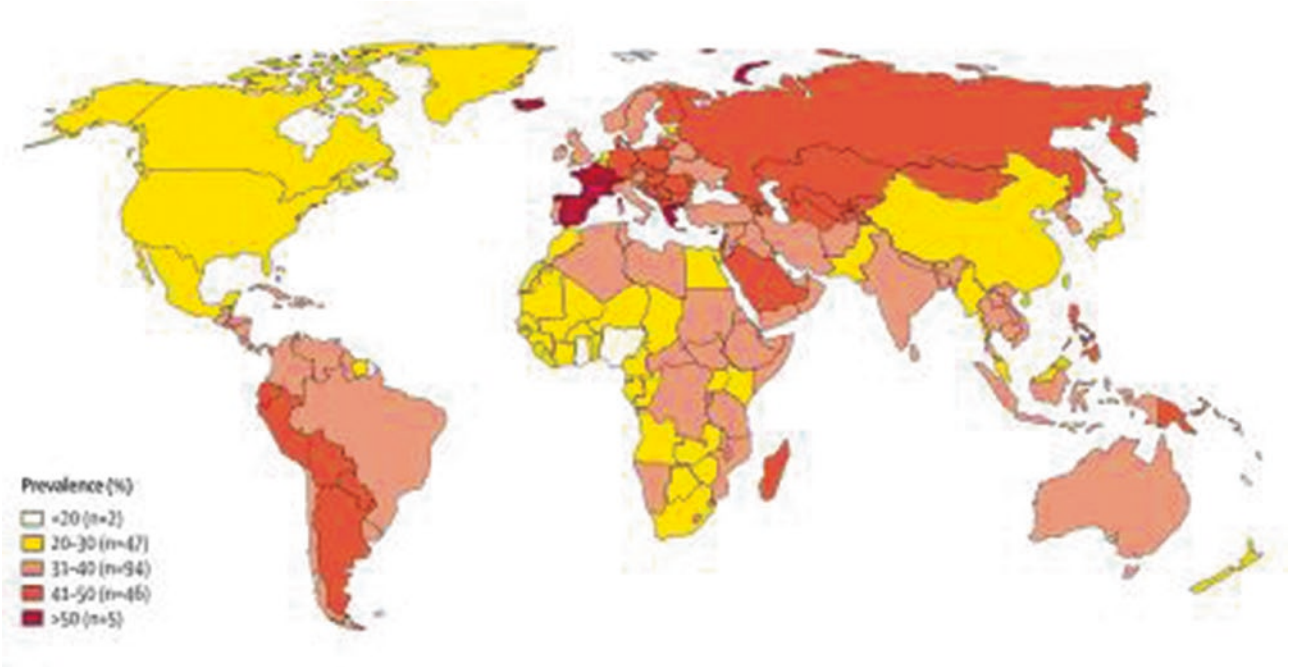


Fig. 3.14 Age-standardised global prevalence of untreated dental caries in Permanent teeth (2017). (Source: Institute of Health Metrics and Evaluation Global Burden of Disease compare tool)

Documented evidence of the burden of untreated caries in the deciduous dentition came from 192 studies which included 1,502,260 children aged 1 to 14 in 74 countries. In 2010, untreated caries in deciduous teeth was the tenth most prevalent condition affecting 9% of the global population; the global age-standardised prevalence was unchangeable between 1990 and 2010 (9%); the age-standardised global incidence was 15,205 cases per 100,000 person-years in 2010 – slight and no significantly less than 15,437 cases per 100,000 cases than in 1990. The lowest age-standardised prevalence was documented in Australia in 2010 (4.8%) and the highest was found in Philippines (10.8%); the highest incidence was shown in Philippines (19,914 per 100,000 person-years), while the lowest was in Australia (8835 cases per 100,000 person-years). The prevalence of untreated caries in deciduous teeth according to the 2015 Global Burden of Diseases Study (GBD) was 7.8%; the age-standardised prevalence rates in 2015 were comparable with the 1990 estimate [47]. The peak of untreated dental caries in deciduous teeth was identified among children aged 1 to 4 years old.

Untreated caries in permanent teeth was the most prevalent condition in 2010 affecting 35% of the global population or 2.4 billion people worldwide. Data came from 186 studies totalling 3,265,546 individuals aged 5 years or older in 67 countries. The global age-standardised prevalence remained stable between 1990 and 2010 at 35%. The age-standardised incidence was 27,257 cases per 1,000,000 person-years in 2010, not significantly different from the 1990 estimates of 28,689 cases per 100,000 person-years. Prevalence reached two peaks, the first at age 25, and another later in life around 70 years – the latter perhaps due to root caries. The lowest age-standardised prevalence was found in Singapore (12%), and the highest was identified in Lithuania (68%). The lowest incidence was in Nigeria (9945 cases per 100,000-person years) and the highest was in Iceland (76,472 cases per 100,000 persons-years) [50]. The 2015 GBD study confirmed that untreated caries in permanent dentition are still the most common condition (34.1%). The peak of untreated dental caries in permanent dentition was found in the 15–19 years old group (Fig. 3.14) [47].

Two published systematic reviews synthesised the epidemiological pattern of a root caries condition. Data from 74 publications revealed a pooled prevalence of 41.5% (95%CI 36.9–46.1 [51], while data from only 20 longitudinal studies showed a pooled annual incidence of 18.25% (95% CI 13.22–23.28) and an increment of 0.45 (0.37–0.43) [52].

Final Considerations

Dental caries continues to be the most widespread chronic disease worldwide affecting children and adults over their life span. The overview of the burden of disease reiterates that this is a major public health problem not only because of its high prevalence but also due to the consequences of its severity on individuals and societies. In this chapter, we covered a range of different dental caries indices and diagnostic criteria employed in epidemiological studies and discussed some advantages and limitations of distinct methods. The use of epidemiology as a tool for the investigation of dental caries has contributed to promoting evidence on the etiological and risk factors related to the disease, its progression and distribution among different populations, and within the same communities over time. The historical changes of the epidemiological patterns of dental caries strongly influenced strategies of its detection, analysis, and control. The continuous and systematic collection, analysis, and interpretation of dental caries-related data serve to inform policy-makers in defining priorities and strategies as well as to generate hypothesis-driven research.

References

1. Holst D, Schuller AA, Aleksejuniené J, Eriksen HM. Caries in populations-a theoretical, causal approach. Eur J Oral Sci. 2001;109(3):143–8.
2. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet. 2007;369:51–9.
3. ten Cate JM, Featherstone JD. Mechanistic aspects of the interactions between fluoride and dental enamel. Crit Rev Oral Biol Med. 1991;2:283–96.
4. Pitts NB, Zero DT, Marsh PD, Ekstrand K, Weintraube JA, Ramos-Gomez F, et al. Dental caries. Nat R Dis Prim. 2017;3:17030.
5. Peres MA, Macpherson LM, Weyant RJ, Daly B, Venturelli R., Mathur MR et al. Oral diseases: a global public health challenge. Lancet. 2019. In press.
6. Klein H, Palmer CE. Dental caries in American Indian children. In: Public Health Bulletin. Washington: Government Printing Office; 1937. Technical Report No 239.
7. American Academy Pediatric Dentistry. Proceedings of the conference: innovations in the prevention and management of early childhood caries. Pediatr Dent. 2015;37(3):198–9.
8. American Academy of Pediatric Dentistry, American Academy of Pediatrics. Policy on early childhood caries (ECC): classifications, consequences, and preventive strategies. Pediatr Dent. 2016;38(6):52–4. Available from: http://www.ingentaconnect.com/content/aapd/pd/2016/00000038/00. Accessed 20/06/2019.
9. Banting DW. The diagnosis of root caries. J Dent Educ. 2001;65:991–6.
10. Featherstone JD. Fluoride, remineralization and root caries. Am J Dent. 1994;7:271–4.
11. Daly B, Watt R, Batchelor P, Treasure E. Overview of epidemiology. In: Essential dental public health. University Press: Oxford; 2002. p. 79–80.
12. Nordblad A. Patterns and indicators of dental decay in the permanent dentition of children and adolescents. Proc Finn Dent Soc. 1986;82(Suppl. 11–13):1–69.
13. Ainsworth NJ. Mottled teeth. Br Dent J. 1933;55:233–50.
14. Gruebbel AO. A measure of dental caries prevalence and treatment service for deciduous teeth. J Dent Res. 1944;23:163–8.
15. Cappelli DP, Mobley CC. Prevention in clinical oral health care. St. Louis: Mosby Elsevier; 2008.
16. Burt BA. How useful are cross-sectional data from surveys of dental caries? Community Dent Oral Epidemiol. 1997;25(1):36–41.
17. Liljestrand JM, Havulinna AS, Paju S, Mannisto S, Salomaa V, Pussinen PJ. Missing teeth predict incident cardiovascular events, diabetes, and death. J Dent Res. 2015;94:1055–62.
18. Bödecker CF. The modified dental caries index. J Am Dent Assoc. 1939;26:1453–60.
19. Broadbent JM, Thomson WM. For debate: problems with the DMF index pertinent to dental caries data analysis. Community Dent Oral Epidemiol. 2005;33(6):400–9.
20. Walsh J. International patterns of oral health care – the example of New Zealand. N Z Dent J. 1970;66(304):143–52.
21. Santamaria RM, Schmoeckel J, Basner R, Schüler E, Splieth CH. Caries trends in the primary dentition of 6- to 7-year-old schoolchildren in Germany from 1994 to 2016: results from the German national oral health surveys in children. Caries Res. 2019;53:659–66.
22. Gupta E, Innes N, Schuller AA, Vermaire JH, Marshman Z. A scoping review of the uses of the care index in children. Community Dent Health. 2017;34(3):131–6.
23. Pitts NB. ICDAS: an international system for caries detection and assessment being developed to facilitate caries epidemiology, research and appropriate clinical management. Community Dent Health. 2004;21(3):193–8.
24. Ekstrand KR, Kuzmina I, Bjørndal L, Thylstrup A. Relationship between external and histologic features of progressive stages of caries in the occlusal fossa. Caries Res. 1995;29(4):243–50.
25. Ekstrand KR, Martignon S, Ricketts DJ, Qvist V. Detection and activity assessment of primary coronal caries lesions: a methodologic study. Oper Dent. 2007;32(3):225–35.
26. Ismail AI, Sohn W, Tellez M, Amaya A, Sen A, Hasson H, et al. The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. Community Dent Oral Epidemiol. 2007;35(3):170–8.
27. Nelson S, Eggertsson H, Powell B, Mandelaris J, Ntragatakis M, Richardson T, et al. Dental examiners consistency in applying the ICDAS criteria for a caries prevention community trial. Community Dent Health. 2011;28(3):238–42.
28. Monse B, Heinrich-Weltzien R, Benzian H, Holmgren C, van Palenstein Helderman W. PUFA – an index of clinical consequences of untreated dental caries. Community Dent Oral Epidemiol. 2010;38:77–82.
29. de Souza AL, Leal SC, Chaves SB, Bronkhorst EM, Frencken JE, Creugers NH. The Caries Assessment Spectrum and Treatment (CAST) instrument: construct validation. Eur J Oral Sci. 2014;122(2):149–53.
30. Pitts NB, Evans DJ, Pine CM. British Association for the Study of Community Dentistry (BASCD) diagnostic criteria for caries prevalence surveys – 1996/97. Community Dent Health. 1997;14(1):6–9.
31. Slade G, Roberts-Thomson K, Ellershaw A. Survey aims and methods. In: Slade GD, Spencer AJ, Robert-Thomson KF, editors. Australia's dental generations: the National Survey of Adult Oral Health 2004–06. AIHW cat. no. DEN 165. Canberra: Australian Institute of Health and Welfare. (Dental Statistics and Research Series No. 34).; 2007. p. 11–36.

32. Barrington G, Khan S, Kent K, Brennan DS, Crocombe LA, Bettiol S. Obesity, dietary sugar and dental caries in Australian adults. Int Dent J. 2019;69:383–91.
33. NHANES. https://www.cdc.gov/nchs/data/nhanes/nhanes/OralHealth_Examiners. Accessed 16/06/2019.
34. World Health Organization. Oral health surveys – basic methods. 5th ed. Geneva: World Health Organization; 2013.
35. Paganelli APD, Constante HM, Sala FS, Bainha CC, Bastos JL, Peres MA. Trends in dental caries rates over 45 years (1971-2016) among schoolchildren in Florianópolis, southern Brazil. Int Dent J. 2018;68(1):47–53.
36. BASCD Public Health England: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/768368/NDEP_for_England_OH_Survey_5yr_2017_Report.pdf.
37. Zhang J, Sardana D, Wong MCM, Leung KCM, Lo ECM. Factors Associated with Dental Root Caries: A Systematic Review. JDR Clin Trans Res. 2019;2380084419849045.
38. Summey DL, Jordan HV, Englander HR. The prevalence of root surface caries in selected populations. J Periodontal. 1973;44(8):500–4.
39. ICDAS. http://www.tordent.com/pdfs/2011/2011exhibitors/concepts-caries-Abrams.pdf. Accessed 27/06/2019.
40. Bratthall D. Introducing the significant caries index together with a proposal for a new global oral health goal for 12-year-olds. Int Dent J. 2000;50(6):378–84.
41. Gini C. On the Measure of Concentration with Special Reference to Income and Statistics, Colorado College Publication. General Series. 1936;208:73–9.
42. Gastwirth JL. The estimation of the Lorenz curve and Gini index. Rev Econ Stat. 1972;54(3):306–16.
43. Campus G, Solinas G, Strohmenger L, Cagetti MG, Senna A, Minelli L, et al. National pathfinder survey on children's oral health in Italy: pattern and severity of caries disease in 4-year-olds. Caries Res. 2009;43:155–62.
44. Haight FA. Handbook of the Poisson distribution. New York: John Wiley & Sons; 1967.
45. Hilbe JM. Negative Binomial Regression. 2nd ed. Cambridge: Cambridge University Press; 2011.
46. Böhning D, Dietz E, Schlattmann P, Mendonca L, Kirchner U. The zero-inflated Poisson model and the decayed, missing and filled teeth index in dental epidemiology. J R Statist Soc Series A. 1999;162(2):195–209.
47. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al. Global, regional, and national prevalence, incidence, and disability-adjusted life years for Oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96:380–7.
48. Broadbent JM, Foster Page LA, Thomson WM, Poulton R. Permanent dentition caries through the first half of life. Br Dent J. 2013;215(7):E12.
49. Peres MA, Sheiham A, Liu P, Demarco FF, Silva AE, Assunção MC, et al. Sugar consumption and changes in dental caries from childhood to adolescence. J Dent Res. 2016;95(4):388–94.
50. Hummel R, Akveld NAE, Bruers JJM, van der Sanden WJM, Su N, van der Heijden GJMG. Caries progression rates revisited: a systematic review. J Dent Res. 2019 May;9:22034519847953.
51. Pentapati KC, Siddiq H, Yeturu SK. Global and regional estimates of the prevalence of root caries – Systematic review and meta-analysis. Saudi Dent J. 2019;31(1):3–15.
52. Hariyani N, Setyowati D, Spencer AJ, Luzzi L, Do LG. Root caries incidence and increment in the population – A systematic review, meta-analysis and meta-regression of longitudinal studies. J Dent. 2018;77:1–7.
53. Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. Int Epidemiol. 2002;31:1091–3.

Further Reading

Phantumvanit P, Makino Y, Ogawa H, Rugg-Gunn A, Moynihan P, Petersen PE, Evans W, Feldens CA, Lo E, Khoshnevisan MH, Baez R, Varenne B, Vichayanrat T, Songpaisan Y, Woodward M, Nakornchai S, Ungchusak C. WHO global consultation on public health intervention against early childhood caries. Community Dent Oral Epidemiol. 2018;46(3):280–7.

Epidemiology of Periodontal Diseases

Vibeke Baelum and Rodrigo López

Contents

4.1 Introduction – 58

4.2 What Do We Understand by 'Periodontal Diseases'? – 58

4.3 Periodontal Disease: Gingivitis and Periodontitis – 59

4.4 Measuring and Recording Gingivitis and Periodontitis – 60
4.4.1 Signs and Symptoms of Gingivitis and Periodontitis – 61

4.5 Describing the Results of Periodontal Epidemiological Studies – 62

4.6 Reporting Standards for Periodontal Epidemiology – 65

4.7 Other Diversity Expressions: Grouping Extent and Severity – 67

4.8 Comparability Within and Between Periodontal Epidemiologic Studies – 67
4.8.1 Different Recording Protocols as Compromising Factors – 68
4.8.2 Disease Levels as Compromising Factors – 68
4.8.3 Validity of Periodontal Recordings – 70

4.9 Sifting the Evidence: Descriptive Periodontal Epidemiology – 70
4.9.1 Age – 71
4.9.2 Gender – 72
4.9.3 Race/Ethnicity – 72
4.9.4 Country/Region – 73
4.9.5 Socioeconomic Factors – 73
4.9.6 Behavioural Factors – 73
4.9.7 Trends in Periodontal Diseases over Time – 73

4.10 The Way Forward in Periodontal Epidemiology? – 74

References – 75

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_4

Learning Objectives

- To provide knowledge of the issues at stake in periodontal disease classification
- To provide knowledge of key methods for the recording of gingivitis and periodontitis
- To provide knowledge of key epidemiologic measures of gingivitis and periodontitis
- To provide a highlight of the obstacles involved in comparisons of results of epidemiological studies of periodontal diseases

4.1 Introduction

Paraphrasing MacMahon and Trichopoulos [1], *periodontal disease epidemiology* can be construed as a discipline concerned with the study of the *distribution* and the *determinants* of the periodontal disease frequency in human populations. As such, two areas of interest can be identified – the study of the distribution of periodontal disease in populations (descriptive epidemiology) and the study of the determinants of the observed distributions (analytical epidemiology). In descriptive epidemiology, we seek to describe the distribution in terms of *demographic characteristics*, such as age, gender, ethnicity, geography, and time; and in analytical epidemiology we seek explanations for such patterns.

It follows from these remarks that *variation in disease occurrence* is at the centre of epidemiology, and in epidemiology we are interested in studying variation within as well as between populations. However, as pointed out by Rose [2], the study of *within-population variation* in disease occurrence will often limit the levels and range of exposures that may be investigated as possible determinants, and this makes comparisons across different populations very important. As Rose [2] phrased it: '*I find it increasingly helpful to distinguish two kinds of aetiological question. The first seeks the causes of cases and the second seeks the causes of incidence*'. However, to identify the determinants of variation in the occurrence of periodontal diseases within and between populations, one must necessarily be certain that the observed differences are real and not attributable to methodological issues. And this is precisely where a lot of problems may arise.

The purpose of this chapter is therefore not to provide (yet) another comprehensive review of the epidemiological findings relating to periodontal diseases but rather to point out the pitfalls that may result in misleading conclusions, and therefore flawed inference, when comparing *epidemiologic estimates* of periodontal diseases within and between populations.

Point of Emphasis

Periodontal disease epidemiology concerns the study of the distribution (descriptive epidemiology) and the determinants (analytical epidemiology) of periodontal disease in human populations

4.2 What Do We Understand by 'Periodontal Diseases'?

It is a historical fact that the term '*periodontal disease*' has had many and rather varied definitions over time. These *periodontal disease definitions* continue to be in flux, resulting in the persistent absence of a uniform understanding of the term even today. The more than 50-year-old note by Scherp [3] still remains valid [4, 5]: '*Discussions of periodontal disease commonly begin with the tacit assumption that all participants are considering the same entity. Since the varieties of periodontal diseases are almost limitless, depending on one's taste for subclassification, this unqualified usage often leads to fruitless semantic misunderstandings*' [3].

The large number of *periodontal disease classification* systems proposed and/or adopted over the past decades [6] is a testament to the continued validity of Scherp's observation. ◘ Figure 4.1 presents the four most recent classification systems for periodontitis that have been adopted by the American Academy of Periodontology. In 1986 [7], a classification system was adopted, which distinguished between *juvenile periodontitis*, *adult periodontitis*, *necrotizing ulcerative gingivo-periodontitis*, and *refractory periodontitis*. In 1989, the term *early-onset periodontitis* was coined to encompass *prepubertal, juvenile*, and *rapidly progressive periodontitis*, just as a category of *periodontitis associated with systemic disease* was added [7]. In the 1999 classification [8], a rather dramatic change was made and the categories *aggressive periodontitis* and *chronic periodontitis* replaced previous categories of *early-onset periodontitis* and *adult periodontitis*, just as a category of *periodontitis associated with endodontic lesions* was added. In the most recent classification system [9] launched in June 2018, the categories of *aggressive periodontitis* and *chronic periodontitis* were abandoned and merged in a single disease category, *periodontitis*, just as *periodontitis as a manifestation of systemic diseases* was removed, and a category of *periodontal abscess* was added.

It is clear that the perpetual reclassifications of periodontal diseases [10] outlined above have served to obfuscate to a considerable degree the scientific evidence base regarding the epidemiology, aetiology, treatment, and prognosis of periodontal diseases [11–14]. Equally problematic is the fact that – with a few notable

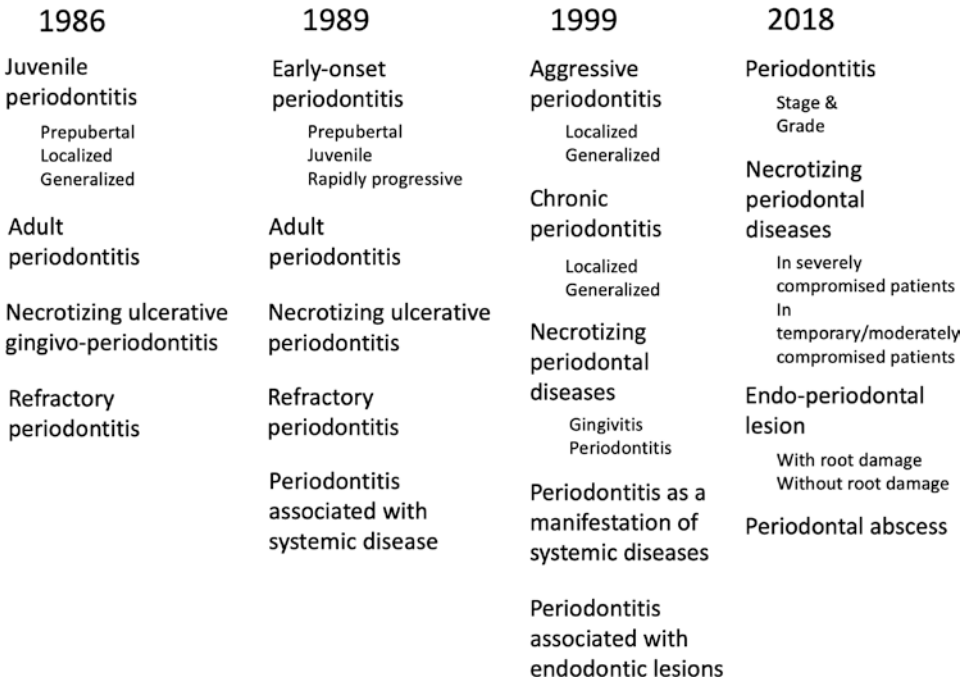


Fig. 4.1 The periodontitis categories defined in the four most recent periodontal disease classification systems adopted by the American Academy of Periodontology [7–9]

exceptions [15, 16] – the periodontal disease classification systems hitherto proposed have generally suffered from the complete lack of *operational diagnostic criteria* for the different disease categories proposed [17]. While this fact has been acknowledged [18, 19], it has never really led to a different approach to *disease classification*. The result has been a multiplicity of disease definitions [4, 5] as researchers have had to deduce the diagnostic distinctions between cases of the different disease entities from descriptions of the 'typical' features of such cases [20], which obviously lend themselves to considerable interpretation [4, 5, 21].

Point of Emphasis

The issue of periodontal disease classification continues to be obfuscated by a lack of clarity about the intended purpose(s) and a general failure to understand that a 'serve-all-purposes-classification' is an unobtainable goal.

4.3 Periodontal Disease: Gingivitis and Periodontitis

The consensus emanating from the most recent periodontal disease classification of June 2018 [9, 16, 22–24] is that the term 'periodontal diseases' encompasses two major disease categories, *gingivitis* and *periodontitis*. Hence, the categories of *aggressive* and *chronic periodontitis* that have been used since 1999 [8] have been merged into a single category of *periodontitis*. Unfortunately, though, the new classification system continues to subclassify gingivitis and periodontitis by tying etiological statements to the disease (sub-)categories, as, for example, when defining '*plaque-induced gingivitis*' [24] or defining cases of periodontitis noting that *'… the observed CAL [clinical attachment loss] cannot be ascribed to non-periodontitis-related causes ….'* [9]. Such etiological ties are downright unhelpful in the context of disease definitions and classifications. This is first of all because the *validity* of the *causal claims* may be questioned as representing little more than clinical impression, conjecture, or best guesses [25]. Moreover, etiological ties, such as considering only periodontal destruction of non-traumatic origin [9], are deleterious because they exclude the possibility of *compound causes*, for example, periodontal destruction with both a traumatic and a dental plaque-related origin. Given the current limitations of the evidence base, it is our view that etiological assumptions should be entirely avoided in the definition of gingivitis and periodontitis and that focus should be turned to considering the cardinal signs and symptoms of gingival inflammation (gingivitis) and destruction of the periodontal attachment apparatus (periodontitis). According to this approach, which is termed *nominalistic* [26–28], the disease name, e.g. 'periodontitis' or 'gingivitis', is merely a label used to describe a group of individuals who share certain defining characteristics [17, 27, 28], and the disease name is just a brief statement of the common abnormality by which the 'gingivitis-' or 'periodontitis' patients can be identified. At the current level of evidence, we find that presumptions about possible causal factors are better made

when deciding on the therapeutic options relevant for the management of a given patient, the clinical particulars of whom might indicate a need for correction of the oral hygiene practices towards less vigorous techniques, or endodontic treatment, restorative therapy, abscess draining, and so on.

More formally, Scadding [28] has defined a disease as '*the sum of abnormal phenomena displayed by a group of living organisms in association with a specified characteristic or set of characteristics by which they differ from the norm for their species in such a way as to place them at a biological disadvantage*', and the actual disease name refers to this sum [27]. While we may define 'gingivitis' and 'periodontitis' as the labels that describe the abnormality from which gingivitis, respectively, periodontitis patients suffer; the sharp reader may wonder about the meaning of 'abnormality' in the context of gingivitis and periodontitis. Interestingly, it has been shown [29] that health professionals are more likely to associate abnormalities with disease connotations than are laypeople, and this is possibly due to the role of the health professional for the diagnosis and treatment of the perceived 'disease'. Scadding [27, 28] was clear that the abnormality should be of such a magnitude that it would place the patient at a biological disadvantage but also recognized that the term 'biological disadvantage' may be a rather vague descriptor. In the context of periodontitis, a 'severe-disease-for-age' yardstick has been proposed [30–32] as a marker of the degree of biological disadvantage caused, but as also pointed out [30, 32], use of such a yardstick as a measure of the threat to the preservation of the teeth in a functional state hinges on a number of assumptions, the validity of which remains unclear. As regards gingivitis, it is now recognized that 'pristine clinical health' is rare [33] owing to the continuous immunological surveillance taking place in the gingiva [23]. It is therefore conceivable that the presence of sites showing evidence of clinical gingival inflammation may to some degree fall within the spectrum of 'clinical health' [23].

Point of Emphasis

In view of the current limitations of the evidence base, etiological assumptions should be entirely avoided in the definition of gingivitis and periodontitis.

4.4 Measuring and Recording Gingivitis and Periodontitis

In view of the state of flux that historically characterizes views and concepts regarding periodontal diseases, it is hardly surprising that the methods used to epidemiologically record and quantify periodontal diseases have also undergone considerable change over time. In the middle of the twentieth century, the results of an epidemiological study by Marshall-Day et al. [34] appeared to support the commonly held view that gingivitis was the impending harbinger of periodontitis, which would ultimately lead to the loss of teeth (Fig. 4.2). This view led to the development of composite epidemiological recording methods, such as the *Russell Periodontal Index* (*PI*) [35], Ramfjord's *Periodontal Disease Index* (*PDI*) [36], or systems originally devised for assessments of periodontal treatment

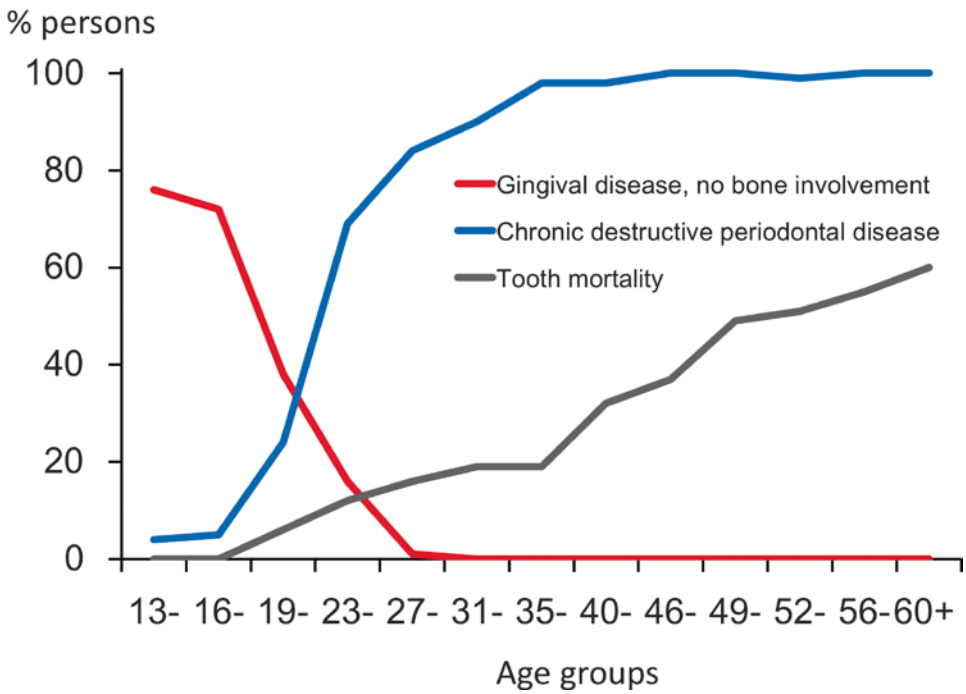


Fig. 4.2 The distribution of gingival disease, destructive periodontal disease, and tooth mortality according to age, as observed by Marshall-Day et al. [34] in 1955

Table 4.1 The criteria of the two – in a historical perspective – most commonly used composite indices for the recording of periodontal diseases

Russell PI [35]		CPITN [38]	
Score	**Condition**	**Score**	**Condition**
0	Negative	0	No signs of disease
1	Mild gingivitis	1	Gingival bleeding after gentle probing
2	Gingivitis	2	Supra- or subgingival calculus
6	Gingivitis with pocket formation	3	Pathologic pocket 4–5 mm
8	Advanced destruction with loss of masticatory function	4	Pathologic pocket ≥ 6 mm
Does not involve probing Recorded for all teeth present Mean score for mouth – then mean score for group		Ten index teeth recorded (17/16, 11, 26/27, 47/46, 31, 36/37) Worst (highest) score for each sextant Worst (highest) score for each person	

needs, such as the *Periodontal Treatment Needs System* (*PTNS*) [37] and its successor, the *Community Periodontal Index of Treatment Needs* (*CPITN*) [38]. The latter was subsequently revised into the *Community Periodontal Index* (*CPI*) [39] and, most recently, into the *modified CPI* [40] which represents a fundamental departure from the hierarchical and composite scoring methods inherent in the CPITN [38] and the CPI [39]. Hence, in the modified CPI [40], *bleeding on probing*, *pocket depths*, and *loss of attachment* severity are recorded independently of each other, and the modified CPI can therefore be regarded as a *partial recording protocol* for the recording of bleeding on probing, two categories of pocket depths and four categories of loss of attachment. The criteria for the two most commonly used composite recording methods in periodontal epidemiology, the Russell PI [35] and the CPITN [38], are shown in Table 4.1.

As these composite methods must now be considered obsolete [41], it should also be acknowledged that many *dogmas* about the epidemiology of periodontal diseases originate in studies using precisely these old-school *composite recording methods* [42, 43]. These dogmas include the ubiquity of periodontal diseases, the linear and continuous progression of periodontal diseases, the much greater severity of periodontal diseases in African and Asian populations than in European and North American populations, and the view that almost all the variation in periodontal disease severity can be explained by a combination of poor oral hygiene and advanced age [42]. From the point of view of analytical periodontal epidemiology, the latter view would seem to render redundant the search for causes of periodontal diseases over and beyond age and oral hygiene.

Fortunately, two smaller studies published in the first part of the 1980s sparked a radical change of views regarding periodontal disease epidemiology. Clinical data presented by Goodson and coworkers [44] indicated that '*the concept of periodontal diseases as slow, continuously progressive diseases should be questioned*', and epidemiological data presented by Cutress and coworkers [45] showed that '*even where plaque accumulation is massive and gingivitis endemic, only a small proportion of individuals are likely to develop alveolar bone loss of sufficient severity to cause major dental breakdown and multiple tooth loss*'. These observations set the scene for periodontal epidemiological studies that abandoned the composite recording methods and turned to the basics of recording the disease parameters separately and expressing the results in such a way that the diversity of responses can be explored.

4.4.1 Signs and Symptoms of Gingivitis and Periodontitis

It is generally agreed that *gingivitis*, by which we understand an inflammatory reaction confined to the gingiva, is usually characterized by subtle clinical changes. It typically goes unnoticed by the patients [46] since it is largely painless (an exception is the unusual necrotizing variant) and only infrequently associated with spontaneous bleeding. The clinical signs of gingivitis comprise bleeding, redness and oedema, and numerous *gingival indices* of varying complexity have been devised to capture these signs and provide measures of gingivitis (for review of the diagnostic methods and indices available for gingivitis, see Trombelli et al. [24]). However, Trombelli et al. [24] also concluded that the gingivitis status of a person *'could be simply, objectively and accurately defined and graded using a BOP score (BOP%)'*. The *BOP% 'is assessed as the proportion of bleeding sites (dichotomous yes/no evaluation) when stimulated by a standardized (dimensions and shape) manual probe with a controlled (~ 25 g) force to the bottom of the sulcus/pocket at six sites mesiobuccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) on all present teeth'* [24]

Periodontitis is first and foremost characterized by the inflammatory destruction of the fibrous periodontal attachment of the teeth (the periodontal ligament) to the alveolar bone. This leads to an apical shift of the junctional epithelium and loss of alveolar bone. This process

may, or may not, be accompanied by pathological deepening of the periodontal pocket. Currently, there are no methods available which allow for the determination of the activity of this destructive process, and this makes it difficult to distinguish the condition of gingivitis in a stable, but reduced, periodontium from the condition of an actively ongoing periodontitis, at any given point in time. However, clinical considerations make it reasonable to classify a person with gingivitis in a stable, reduced periodontium as a case of periodontitis [47, 48].

The defining characteristic of past or ongoing periodontitis is *clinical attachment loss* (*CAL*), detected by *'circumferential assessment of the erupted dentition with a standardized periodontal probe with reference to the cemento-enamel junction (CEJ)'* [9]. While circumferential probing may be feasible in a clinical setting, most epidemiological studies are based on the use of a *partial recording protocol*, according to which predefined sites (e.g. the buccal and mesiobuccal sites [49]; the mesial, buccal, distal, and lingual sites [50] or even six sites per tooth [51, 52]) are assessed in all teeth present (which may or may not include third molars) or in predefined subsets of teeth [40, 53].

The CAL can be determined in different ways [54], either as a direct, single measurement in mm of the distance from the CEJ to the bottom of the clinical pocket or as an indirect calculation based on two measurements: the *probing pocket depth* (*PPD*) and the amount of *recession* of the gingival margin (*REC*). The recession measurement is recorded as negative or positive depending on the position of the gingival margin relative to the CEJ. Occasionally, the two methods are combined so that *direct CAL measurements* are taken, when REC is present, whereas CAL is calculated when the CEJ is covered by gingiva [22, 55]. We strongly recommend the direct method for assessing the CAL owing to the observation that direct CAL measurements are associated with less measurement error than those obtained with the *indirect method for CAL estimation* [54]. Even so, many prefer use of the indirect method [49, 51].

While many clinicians still prefer to look at *radiographic bone levels* rather than do CAL assessments [56], this practice is fortunately not an option in periodontal epidemiology owing to the size of epidemiological studies. Radiographs are insufficient *diagnostic tools* as they are insensitive to early bone loss and to bone loss in buccal and oral sites, just as radiography is potentially harmful [57].

Point of Emphasis

The defining characteristic of past or ongoing periodontitis is clinical attachment loss, which is most rationally determined using direct, single measurements in mm of the distance from the CEJ to the bottom of the clinical pocket.

4.5 Describing the Results of Periodontal Epidemiological Studies

It follows that epidemiological studies of both gingivitis and periodontitis may involve the recording of the periodontal characteristics of BOP, CAL, PPD, or REC in up to 28 teeth × 6 sites = 168 sites *per person* examined, if third molars are excluded, and in up to 192 sites *per person* if third molars are included in the examination. For each of the characteristics BOP, CAL, PPD, and REC, the recordings made in a given person are summarized by the parameters of *Presence* and *Extent* (► Box 4.1):

- Presence – Does the person have sites with BOP/CAL/PPD/REC?
- Extent – What number/proportion of sites in the person have BOP/CAL/PPD/REC?

For the recordings of CAL, PPD and REC, an additional dimension of *Severity* is relevant:

- Severity – How severe/deep are the recordings of CAL/PPD/REC at the sites?

Box 4.1

The three dimensions characterizing the periodontal status in a person

Presence	Does the person have BOP/CAL/PPD/REC in one or more sites?
Extent	How many sites/what proportion of sites are affected?
Severity	How severe/deep is the CAL/PPD/REC?

There are two principally different approaches to the summary of the periodontal recordings in each person:

- Calculate the *mean value* of the measurements made in the sites recorded in the person (mean BOP score/mouth, mean CAL/mouth, mean PPD/mouth, mean REC/mouth).
- *Count* the number of sites affected by BOP or by CAL or PPD or REC exceeding predefined threshold values, e.g. ≥ 4 mm, and express these as absolute or relative numbers (# sites affected/# sites recorded).

However, the calculation of the mean CAL or the mean PPD/REC for the individual involves an amalgamation of the dimensions of *Extent* and *Severity* (how many sites are affected by how much), and this mean value therefore tends to attenuate the variation across the dentition.

At the group/population level, which is the level of focus in periodontal epidemiology, the three questions of ► Box 4.1 translate into measures of *prevalence*, *dis-*

tribution of extent, and *distribution of severity* of the recordings shown in ▶ Box 4.2. Since multiple thresholds for CAL, PPD and REC may be employed with each of these measures, a multitude of parameters can be derived in the description of the results of periodontal epidemiological studies. Such data are most conveniently presented in graphical form through *cumulative frequency distributions*.

Box 4.2
The three dimensions characterizing the periodontal conditions in a population

Prevalence	What proportion of people have BOP/CAL/PPD/REC?
Distribution of extent	What is the distribution of people according to the absolute number or the proportion of sites affected by BOP/CAL/PPD/REC?
Distribution of severity	What is the distribution of people according to the severity of the CAL/PPD/REC?

Figures 4.3a–h show the cumulative frequency distributions of the examinees according to selected count-based periodontal parameters for 10-year age groups in an adult rural Chinese population [58, 59]. The panels on the left-hand side (Fig. 4.3a–d) illustrate the distribution of dentate examinees according to the *proportion* of sites/mouth that have a CAL recording at or exceeding the thresholds of 1, 3, 5, and 7 mm, respectively, whereas the panels on the right-hand side (Fig. 4.3e–h) show the distribution of dentate examinees according to the *absolute number* of sites/mouth affected by such CAL recordings.

These graphs illustrate a very important feature of periodontitis observed in populations [50, 53, 60–62]: the distribution of clinical attachment loss follows a *continuum of disease severity* such that absence or low severity of clinical attachment loss merges imperceptibly into high severity of clinical attachment loss. In other words, there is no sharp or natural distinction between health and disease or between milder or more extensive disease expressions. If follows that setting thresholds for periodontitis disease extent and severity will invariably involve arbitrary decisions.

The age-specific prevalence estimates may be read as the percentage values on the *y*-axis corresponding to the top-left starting points of each curve. The figure shows that the prevalence of CAL ≥ 3 mm is 100% in all but the youngest age group (Fig. 4.3b, f) and the prevalence of CAL ≥ 5 mm is 60% among 30–39-yr-olds, increasing to 95% among the 70+-yr-olds (Fig. 4.3c, g). Moreover, any desired percentile value can be read off or marked in the curves. As an example, the median values can be found by determining the *x*-axis values corresponding to 50% on the *y*-axis for each curve.

These cumulative distribution graphs also illustrate *skewedness* as an important distributional feature of most periodontal epidemiologic data. Had the data followed a *Gaussian (normal) distribution*, these cumulative curves should have assumed the shape of an inverse S, and this feature is only approximately fulfilled for the distribution of the number of sites per mouth with CAL ≥ 3 mm (Fig. 4.3f). For all other parameters shown, skewedness is rather pronounced, and the shape of the curves for the same periodontal parameter (e.g. % sites per mouth with CAL ≥ 3 mm, Fig. 4.3b) differs across age groups. This skewedness impacts on the options available for data presentations. While the mean value would be a very convenient summary estimator for any periodontal parameter that follows a Gaussian distribution (or, as a minimum, an approximately symmetrical distribution, as shown in Fig. 4.3f), it is not meaningful when there is marked *skewedness* in the distributions of the parameter. One would therefore have to turn to *percentile-based summaries* of the distributions (e.g. *median values, interquartile ranges*, extreme percentile). These are clearly less convenient than using the *mean* and *standard deviations* as summaries of *central tendency* and *variation*, but they are much better descriptors when distributional skewedness is pronounced.

The decision whether to present the distribution of the proportion of sites affected (Fig. 4.3a–d) or the distribution of the absolute number of sites affected (Fig. 4.3e–h) is essentially determined by the message that one would want to stress. Use of the absolute numbers would illustrate the distribution of the total burden of the signs of periodontal disease. Figure 4.3e shows that the total number of sites with CAL (i.e. ≥ 1 mm) is clearly greatest among the 30–39-yr-olds and lowest among the 70+-yr-olds. However, the number of sites with CAL ≥ 3 mm is fairly even among the youngest and the oldest age groups (Fig. 4.3f), whereas the number of sites with CAL ≥ 7 mm is clearly highest among the 70+-yr-olds and lowest among the 30–39-yr-olds (Fig. 4.3h). When the proportion of sites affected is considered, it is a common observation for all CAL thresholds that a clear and consistent *age gradient* is present with the 70+-yr-olds being the most affected people and the 30–39-yr-olds the least affected (Fig. 4.3a–d).

Even though one may elect to illustrate the distribution of the values of mean CAL/mouth or mean PPD/mouth, as shown in Fig. 4.4a, c, the use of these mouth summaries tends to attenuate the variation observed relative to that observed when presenting the absolute number or the proportion of sites with CAL or PPD exceeding the predefined threshold values of interest (Fig. 4.4b, d).

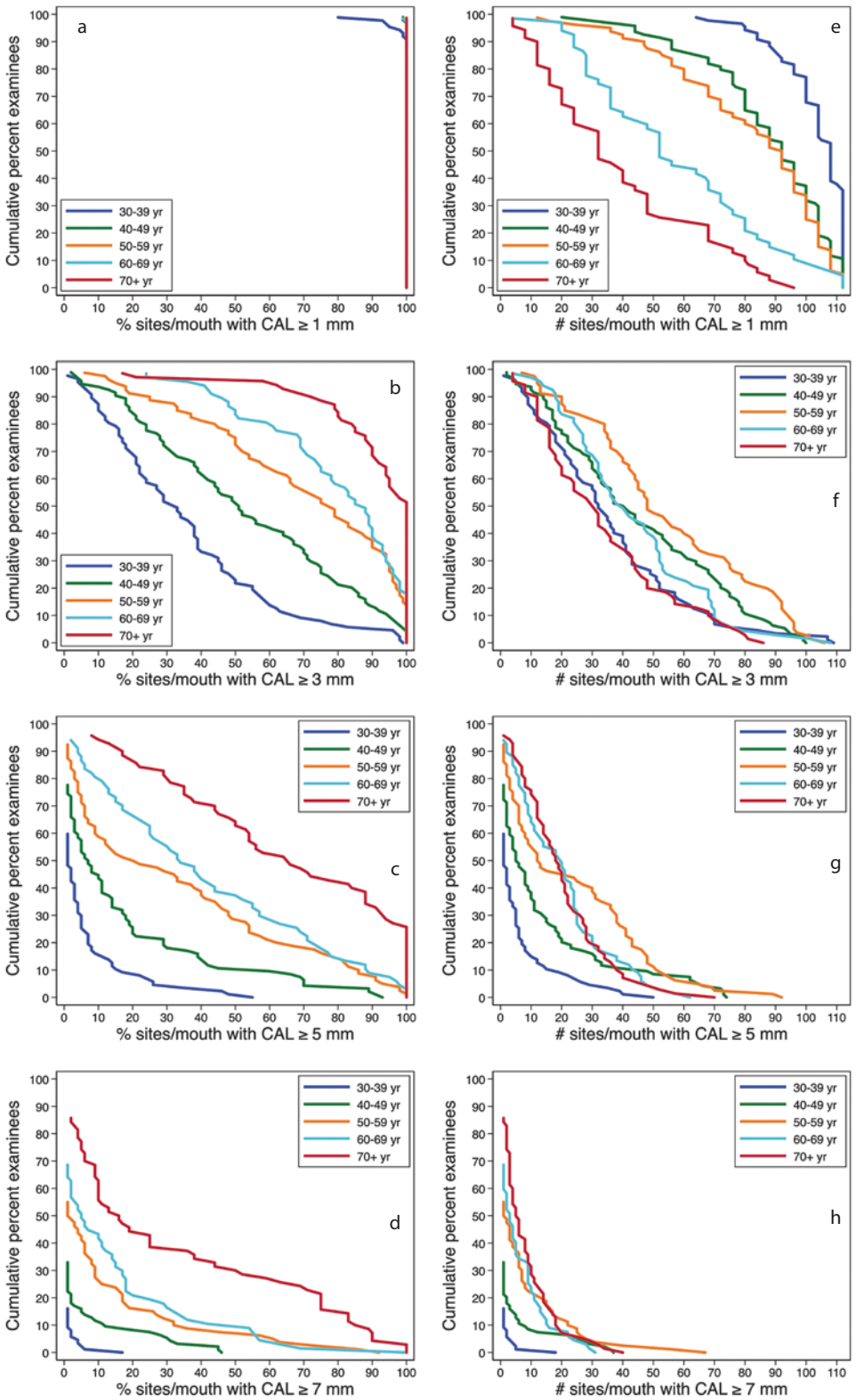


Fig. 4.3 Cumulative frequency distributions of various periodontal disease parameters based on clinical attachment loss (CAL) recordings. In the top row panels **a**, **e**, the threshold considered is CAL ≥ 1 mm, followed by CAL ≥ 3 mm, CAL ≥ 5 mm, and CAL ≥ 7 mm in the ensuing rows. In the left-hand side panels **a**–**d**, extent is expressed as the % sites/mouth, while in panels **e**–**h**, the absolute number of sites/mouth is considered. (Based on data for adult and elderly Chinese [58–60]

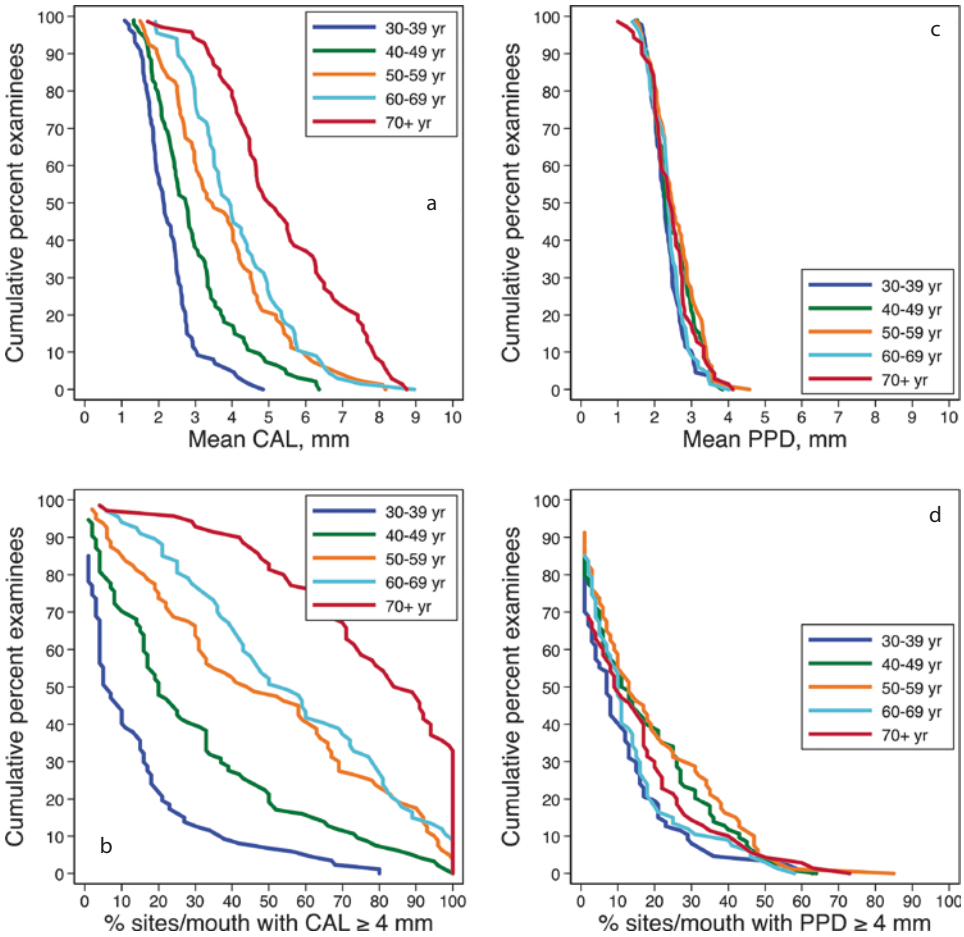


Fig. 4.4 Examples of cumulative frequency distributions for different age groups. In panel **a**, the mean clinical attachment loss (CAL) per mouth is shown. In Panel **b**, the % sites/mouth with CAL ≥ 4 mm is shown. Note that the variability according to age is much greater in Panel **b** than in **a**. Panel **c** shows the cumulative frequency distributions of the mean probing pocket depth (PPD) according to age. Hardly any variation with age is observed. In Panel **d**, which shows the cumulative frequency distributions of the % sites/mouth with PPD ≥ 4 mm, a little variation with age may be discerned. Based on data for adult and elderly Chinese [58–60]

Point of Emphasis

The cross-sectional epidemiological characterization of periodontitis in a population involves three dimensions: the prevalence (the proportion of people with the outcome of interest); the distribution of extent (the distribution of people according to the absolute number or the proportion of sites with the outcome of interest); and the distribution of severity (the change in the distribution of extent with changing thresholds for the outcome of interest).

4.6 Reporting Standards for Periodontal Epidemiology

Owing to the multitude of parameters that may be considered for the characterization of periodontitis [63], a *reporting standard* has been proposed for epidemiologic studies of periodontitis [64] to ensure some degree of comparability in the reporting of results. According to this standard, periodontal epidemiologic reports should include prevalence and extent estimates at both site and tooth level for PPD ≥ 4 mm and PPD ≥ 6 mm, and for CAL ≥ 3 mm and CAL ≥ 5 mm, as well as the estimates of the mean PPD and the mean CAL [64]. While one may sympathize with the idea underpinning the suggestion of a reporting standards, it is not clear that this universal reporting standard will suffice.

The results presented in Table 4.2, which summarizes the results of the epidemiologic study carried out among adult rural Chinese [58, 59], the results of which are also shown in Figs. 4.3 and 4.4, highlight some of the problems in a 'one-size-fits-all' reporting standard. First of all, there is an issue with the preselected *thresholds* for CAL (3 and 5 mm) and PPD (4 and 6 mm). Even though these were selected based on the idea that '*Using these thresholds, prevalence estimates generally do not converge towards 0 or 100%, even in younger or older cohorts so that variation across age groups can be detected*' [64], the results presented in Table 4.2 clearly show that the *prevalence* estimates, particularly for the two CAL thresholds but also for PPD ≥ 4 mm, may reach a

Table 4.2 A selection of the parameters that are part of the recommended reporting standards for epidemiological studies of periodontitis [64], including the estimates according to age as observed in an adult rural, Chinese population [58]

Parameter	Unit	Age group				
		30–39 yr	40–49 yr	50–59 yr	60–69 yr	70+ yr
Examinees	N	87	95	84	84	90
Edentulous[a]	*n* (%)	0 (0%)	1(1%)	4 (5%)	17 (20%)	20 (22%)
Tooth count in dentate[a]	Mean (SD)	27.0 (2.0)	23.3 (4.8)	21.8 (5.9)	15.9 (7.1)	10.5 (6.8)
Prevalence CAL ≥ 3 mm	%	99	100	100	100	100
Prevalence CAL ≥ 5 mm	%	61	79	94	96	97
% sites CAL ≥ 3 mm	Mean (SD)	36 (24)	53 (29)	70 (28)	79 (21)	91 (16)
% sites CAL ≥ 5 mm	Mean (SD)	6 (11)	17 (23)	33 (32)	41 (31)	63 (32)
Mean CAL, mm	Mean (SD)	2.3 (0.8)	3.0 (1.2)	3.8 (1.6)	4.2 (1.4)	5.4 (1.7)
Prevalence PPD ≥ 4 mm	%	80	88	93	87	70
Prevalence PPD ≥ 6 mm	%	15	27	31	13	20
% sites PPD ≥ 4 mm	Mean (SD)	11 (14)	17 (17)	19 (18)	14 (14)	15 (17)
% sites PPD ≥ 6 mm	Mean (SD)	1 (2)	1 (2)	1 (3)	1 (3)	1 (3)
Mean PPD, mm	Mean (SD)	2.3 (0.5)	2.5 (0.6)	2.6 (0.6)	2.4 (0.5)	2.5 (0.6)
No periodontitis[b]	%	25	5	6	1	0
Mild periodontitis[b]	%	0	0	0	0	0
Moderate periodontitis[b]	%	25	10	5	3	0
Severe periodontitis[b]	%	49	85	89	96	100

[a]Excluding third molars
[b]According to the CDC-AAP criteria [65, 66]

saturation level (100%) already from relatively early ages. Variation across age groups is reflected only in the two mean extent estimates for the CAL thresholds (% sites with CAL ≥ 3 mm, respectively, ≥ 5 mm) which do seem to pick up some of the expected variation across age groups. Owing to these issues, as well as other methodological issues that will be dealt with later, we would therefore recommend that between-population comparisons, if desirable, be made on the basis of adapting the analysis of the 'new data set' to match the recording protocols and analyses already made for the data sets to which one wants to compare [67–69].

In Table 4.2, we have presented mean values as recommended in the proposed reporting standard [64] but have elected to accompany these with the standard deviations, rather than standard errors recommended [64]. This is done purposefully to alert the shrewd reader to the fact that the mean extent estimates for pocketing (PPD ≥ 4 mm or PPD ≥ 6 mm) and also for CAL in the younger age groups, are associated with standard deviation estimates that are either of the same magnitude as or even greater than the estimated mean value. This is a clear sign of the mean value being a very poor depiction of the typical observations in the group, and this information on the distributional skewedness would go lost if only standard errors are reported. This is precisely why a graphical presentation of the data can be much more informative, as this allows the expression of the diversity of responses represented in the typically rather skewed distributions of the observations. Alternatively, one could elect to present relevant percentile points for each age group, or even age-related percentile charts, as has been suggested [70].

Point of Emphasis

It is unlikely that any prespecified reporting standard will be universally valid, and between-population comparisons are better made by matching the analysis of the 'new data set' to the recording protocols and analyses already made for the data sets to which one wants to compare.

4.7 Other Diversity Expressions: Grouping Extent and Severity

Other attempts to express the diversity of the gingivitis and periodontitis responses in population groups include the subclassification of the examinees into distinct periodontal disease categories, typically involving labelling adjectives such as 'mild', 'moderate', 'severe', 'established', 'advanced', 'localized', or 'generalized' [8, 23, 24, 65, 66, 71, 72] or the use of 'sensitive' and 'specific' definitions of a periodontitis case [73]. Such groupings may be based on simple criteria, e.g. as when based on the presence of CAL or PPD exceeding a predefined threshold [4, 5], or they may involve rather more complex algorithms [65, 66, 73], as shown in Table 4.3. As regards gingivitis, the most recent reviews [23, 24] suggest that a gingivitis case for epidemiological purposes be defined as a person whose BOP% exceeds 10%, and that the extent may be deemed 'localized', if the BOP% <30%, and 'generalized' when the BOP% ≥ 30%.

Ideally, using such groupings would facilitate comparisons of disease estimates between epidemiological surveys, though clearly under the proviso that the recording methods used in the surveys are otherwise comparable. However, as shown in Table 4.2, these grouping may still suffer the problem of saturation already from early ages. Hence, after the age of 40 years, virtually all the dentate adult rural Chinese examined would be classified as having 'severe' periodontitis according to the CDC-AAP classification system [65, 66, 74] for periodontal surveillance.

Table 4.3 Examples of algorithms used in periodontal epidemiology to classify periodontitis according to CAL and PPD recordings [65, 66, 73]

Periodontitis label	CAL recordings	PPD recordings
Severe	≥ 2 proximal sites with CAL ≥ 6 mm (not on same tooth) *AND*	≥ 1 proximal site with PPD ≥ 5 mm
Moderate	≥ 2 proximal sites with CAL ≥ 4 mm (not on same tooth) *OR*	≥ 2 proximal sites with PPD ≥ 5 mm (not on same tooth)
Mild	≥ 2 proximal sites with CAL ≥ 4 mm (not on same tooth) *AND*	≥ 2 proximal sites with PPD ≥ 4 mm (not on same tooth) *OR* one site with PPD ≥ 5 mm
Sensitive	Presence of proximal CAL ≥ 3 mm in ≥ 2 nonadjacent teeth	–
Specific	Presence of proximal CAL ≥ 5 mm in ≥ 30% of teeth present	–

Point of Emphasis
Grouping periodontitis extent and severity under labels may lead to masking of the variability of these features.

4.8 Comparability Within and Between Periodontal Epidemiologic Studies

Between-group and between-population comparisons are central for inference in periodontal epidemiology. We wish to compare across age, gender, race, geography, and time in order to gain insights into the determinants of prevalence, extent, and severity of the diseases. Moreover, analytical periodontal epidemiology hinges on the existence of real variation in the periodontal disease parameters within and between populations, because it is through attempts to explain this variability that understandings may be gained of the determinants of the diseases.

Unfortunately, a myriad of methodological issues may compromise the *validity of inferences* from such comparisons. Ideally, the comparison of the results of periodontal epidemiological studies across populations or within subgroups of a given population are based on data collected using similar methodologies. These would include similar and representative *sampling methods* [75, 76], (hopefully resulting in) similar and high *participation rates* [77], because the observed disease estimates are necessarily conditioned on study participation. Observed disease estimates represent a mix of forces that determine disease occurrence and forces that determine study participation [78]. If, therefore, study participation is related to factors that determine disease occurrence (which is quite likely), the disease estimates will not be valid and measures of the effect of the determinants will be subject to *collider bias* [78].

Comparability within and between studies also rest on the use of identical *recording protocols* [79] and identical equipment [80], the same set of *calibrated examiners* [81], and the same data analytical and reporting approaches [64]. While these factors are likely to be relatively standardized within a given study, this is typically not the case across different studies, and differences attributable to these factors may compromise

valid inference regarding observed *within- or between-population* differences [82] and thereby mislead the results of analytical periodontal epidemiologic studies.

4.8.1 Different Recording Protocols as Compromising Factors

The data shown in Table 4.2 and Fig. 4.3a–h were based on the recording of four sites per tooth of all teeth present, excluding third molars, leading to a maximum of 112 (= 4 × 28) recordings per examinee per periodontal parameter. As previously alluded to, the number of recordings per person per periodontal parameter may be as high as 192 (32 teeth recorded at 6 sites per tooth, as is the 'gold standard' protocol for the clinical assessment of periodontal diseases [9]), or, as is typical in periodontal epidemiology, it may be substantially reduced due to the use of some form of a *partial recording protocol* [83]. The use of partial recording protocols inevitably results in underestimation of the prevalence of CAL [79, 83, 84] and PPD [79, 84]. Partial recording protocols may also result in biased estimates of both the mean CAL and the mean PPD values [79, 85], as well as biased extent estimates for both CAL and PPD [85]. Moreover, these biases may be sizeable [83, 86] and directed towards over- and underestimation [85] of the true values, depending on the actual recording protocol in question. If partial recording protocols are to be used, the half-mouth six-sites, the diagonal quadrants six-sites, or the full-mouth three-sites (mesiobuccal, buccal and distobuccal) protocols would seem preferable [79] as they seem to be the least biased protocols. Nonetheless, indications are that the comparability of the results of periodontal epidemiological studies employing different recording protocols may be compromised, no matter whether the estimates considered are estimates of prevalence, extent, or severity of disease.

4.8.2 Disease Levels as Compromising Factors

Even if the above factors could indeed be standardized across studies, two additional factors must be considered, which may seriously affect comparability of periodontal disease estimates:

- Differences in tooth retention
- Differences in the extent and severity of gingival inflammation

If the tooth retention rates differ between two populations (or between population subgroups, or in a group followed over time [87]), assumptions must necessarily be invoked regarding the impact of the tooth loss difference when comparing the periodontitis estimates across the two populations. There is ample epidemiological evidence showing that in any given age group, an inverse relationship exists between the observed number of teeth present and the mean CAL (and to some extent also the mean PPD values) in the retained teeth [68, 69]. In other words, the more teeth present, the lower the mean CAL. This gradient is seen both in populations with extensive variation in the extent of tooth retention [68, 69] and in populations where there is only very little variation in the overall large number of teeth present [50, 88] (Fig. 4.5).

Two rather different interpretations may be offered for the higher mean CAL among persons with fewer teeth present:

- The observed CAL is an inflated estimate of what would have been observed had the tooth loss not occurred. This would be the case if the teeth lost (and therefore unobserved for CAL) were relatively unaffected by CAL.
- Alternatively, the teeth may have been lost precisely due to CAL (periodontitis), in which case the observed CAL on the 'healthy survivor'-teeth [89] is likely to underestimate what would have been observed had a number of teeth not been lost already.

Unfortunately, the reasons why teeth are lost is difficult to ascertain [90], particularly in populations with considerable access to dental health care provision where changing dental treatment paradigms [91, 92], treatment strategic considerations [93, 94], and patient preferences [95] are important determinants of the loss of natural teeth [96]. This means that in the face of different *tooth retention* rates among the groups to be compared, it may be rather difficult to ascertain validity of conclusions regarding the meaning of different periodontal disease estimates [82].

The results of the five repeated cross-sectional studies of periodontal diseases over the period 1973–2013 among adults from Jönköping, Sweden [97–99], may be used to further illustrate the complex explanations for the periodontal disease estimates when tooth retention rates change in a population. As shown in Fig. 4.6, the adult population in Jönköping, Sweden, has experienced a dramatic increase in tooth retention over the period 1973–2013. In 1973, the average dentate 70-yr-old had 13.3 teeth present, whereas this estimate had risen to 21.1 teeth for the average dentate 70-yr-old in 2013 [98]. Similarly, edentulism in at least one jaw has reduced among 70-yr-olds from 54% in 1973 to just 4% in 2013 [100]. Over the same 40-year period, the prevalence of moderate or severe periodontitis (grading based on radiographic assessments of the alveolar bone loss as

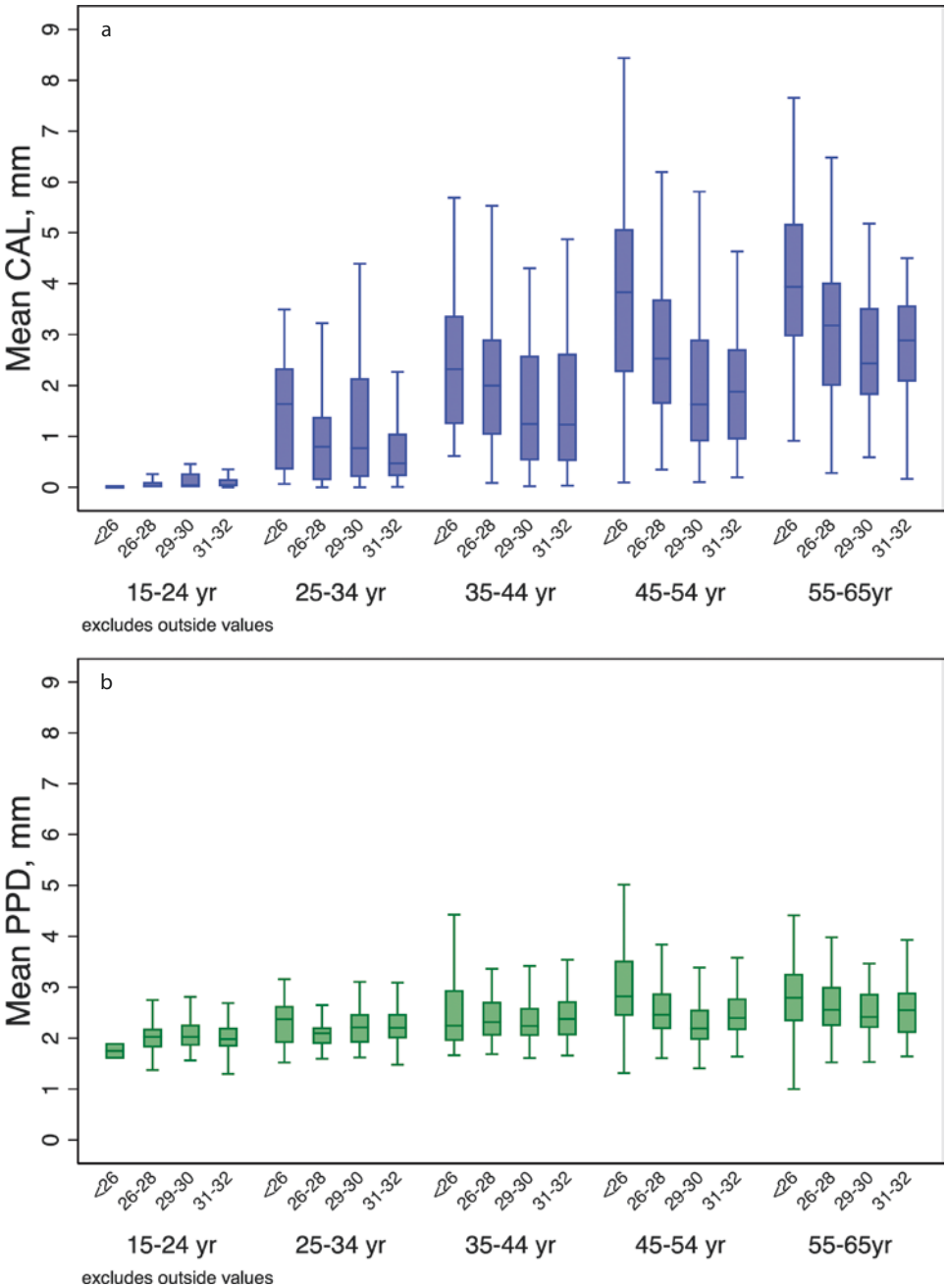


Fig. 4.5 Box plots showing the distribution of the mean clinical attachment loss, CAL (Panel **a**) and the mean probing pocket depth, PPD (panel **b**) according to the number of teeth present for adult Kenyans aged 15–65 year [50, 88]. The boxes denote the median, and interquartile values, while the whiskers indicate lower, respectively, higher adjacent values

exceeding $\frac{1}{3}$ of the root length) increased pronouncedly among the 50-, 60-, and 70-yr-olds between 1973 and 1983, while the occurrence of health or gingivitis either declined (50-yr-olds) or appeared fairly stable at low levels (60- and 70-yr-olds). However, between 1983 and 2003 the prevalence of health or gingivitis increased among the 50-, 60-, and 70-yr-olds, while the prevalence of moderate or severe periodontitis was stable between 1983 and 1993, after which a trend for decline was noted (Fig. 4.7). There can be little doubt that the disease estimates quoted here are influenced by opposing trends in the form of improved oral hygiene leading to less disease on the one hand and on the other hand the increased retention of periodontally diseased teeth resulting from changing treatment paradigms and decreased caries experience. Support for this conclusion may further be found in the observation that the increase in tooth retention between 2003 and 2013 largely resulted from increased tooth retention among people with severe periodontitis [98].

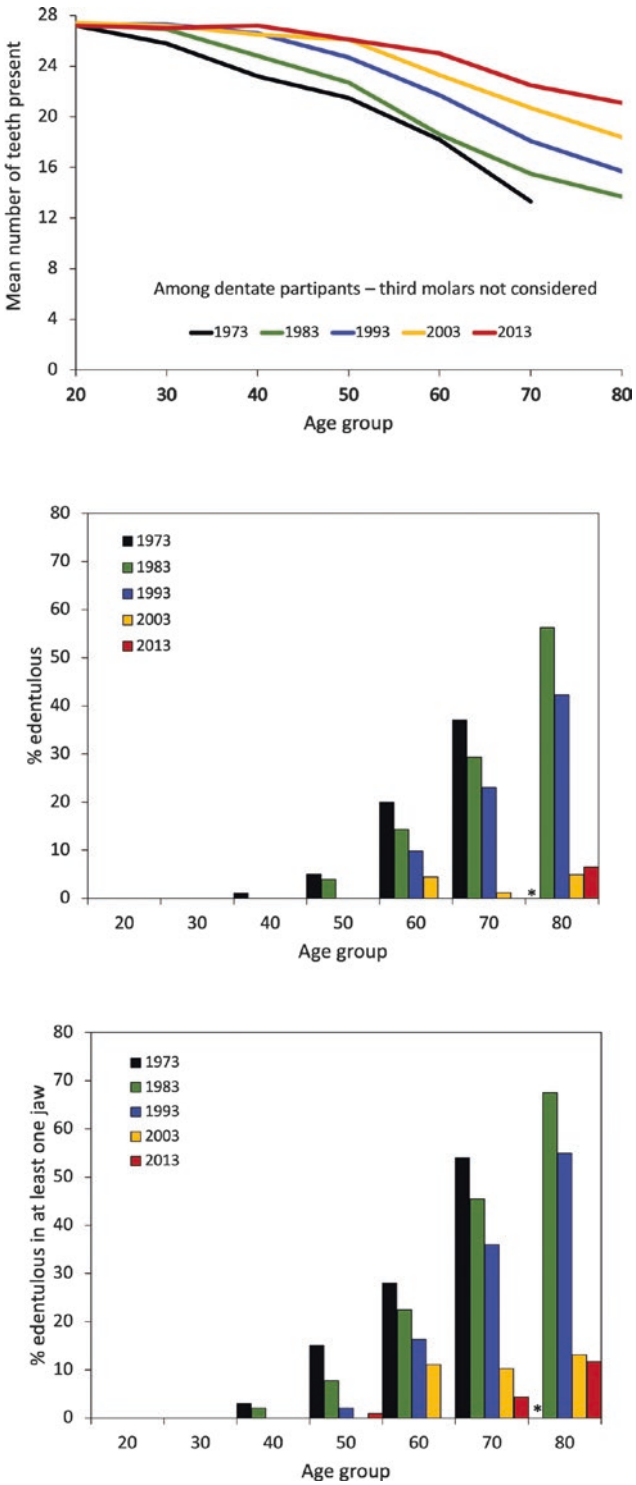


Fig. 4.6 The results of five repeated cross-sectional studies of tooth retention among adults from Jönköping, Sweden [98, 100]. At each survey, approximately 100 adults aged 20, 30, 40, 50, 60, 70, and 80 (not included in 1973) years were examined clinically for the number of teeth present (third molars not included)

4.8.3 Validity of Periodontal Recordings

The clinical assessment of periodontitis is based on probing, and it is well known that the validity of the measurements of CAL and PPD are influenced by factors such as probing pressure [101, 102], probe characteristics [80, 103], and the degree of inflammation in the tissue [101–106]. It is a fact that the probe penetrates into the connective tissue attachment when inflammation is marked and thereby overestimate the amount of attachment lost, while the probe does not reach the apical part of the junctional epithelium when there is little or no inflammation. This means that differences in the inflammatory status of the tissues will manifest themselves in differences in the recordings of the amount of attachment lost, and the prevalence and extent of gingivitis is therefore likely to influence the estimates of the prevalence, extent, and severity of periodontitis in the population. Unfortunately, as far as we are aware, the magnitude of the bias in epidemiological estimates of periodontitis that might be attributable to the extent and severity of gingival inflammation compromising the validity of CAL and PPD recordings has never been investigated, but studies [101] indicate an average CAL difference when probing healthy, respectively, severely inflamed periodontal tissues in the order of magnitude of 1.38–1.55 mm, depending on the probing pressure used.

Point of Emphasis

The comparability of disease estimates across studies is heavily influenced by a wealth of factors, and great care must be exercised and profound methodological insights demonstrated when making inference about similarities and differences of results from different studies.

4.9 Sifting the Evidence: Descriptive Periodontal Epidemiology

Clearly, the above remarks should be taken to indicate that *comparability* of periodontal disease estimates across studies can be heavily compromised, and one must therefore be very cautious when attempting to arrive at general conclusions based on the existing epidemiological evidence. Numerous *reviews*, both *systematic* [75, 82, 107–113] and *narrative* [41, 76, 77, 87, 89, 114–139], have been conducted over the past two decades. Some of these have addressed a specific epidemiological question, such as the rate of periodontitis

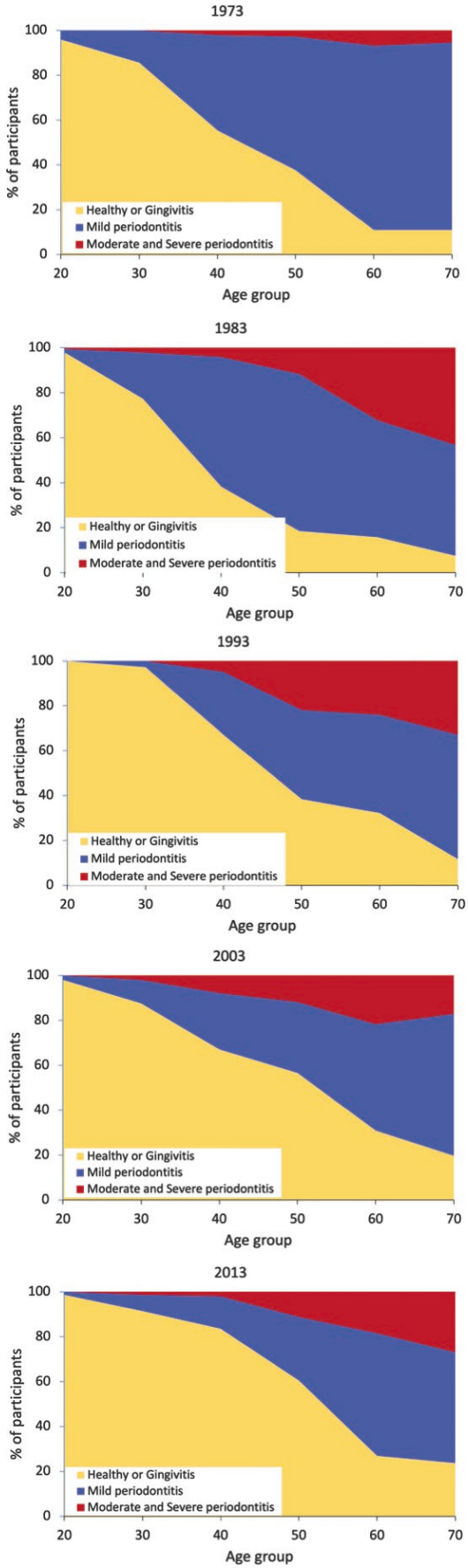


Fig. 4.7 The results of five repeated cross-sectional studies of periodontal diseases among adults from Jönköping, Sweden [98, 99]. At each survey, approximately 100 adults aged 20, 30, 40, 50, 60, and 70 years were examined clinically and radiographically and classified according to periodontal disease severity. Healthy, bleeding on gentle probing in < 20% of sites; gingivitis, bleeding on gentle probing in ≥ 20% of sites, normal alveolar bone height; mild periodontitis, alveolar bone loss predominantly < $\frac{1}{3}$ of the root length; moderate periodontitis, alveolar bone loss predominantly between $\frac{1}{3}$ and $\frac{2}{3}$ of the root length; severe periodontitis, alveolar bone less predominantly > $\frac{2}{3}$ of the root length, including angular bony defects and furcation defects

progression [82], identification of *high-risk groups* and individuals [129], time *trends* in periodontitis prevalence [116, 124, 125], the effect of oral hygiene [108], gender [113], frequency of tooth brushing [112], nutrition [114], and socioeconomic position [110, 121], while most other reviews have been more 'global' in their account of the epidemiological features of periodontal diseases. The majority of the reviews are concerned with periodontitis, and reviews considering *gingivitis epidemiology* are less frequent [41, 118, 119, 131, 135, 139]. As the brief account in the following will show, the aforementioned reviews do not agree unanimously in their conclusions with respect to the epidemiologic estimates for groups defined by key demographic, social, and behavioural factors. It is therefore prudent to note that in virtually all reviews cited, reservations are commonly expressed with respect to the conclusions drawn, or it is even determined that no conclusive statements can be made about specific aspects of the epidemiology of periodontitis. Hence, most reviews refer to the possibility of distorting effects of the considerable variability in methodology and quality of the original studies under review [41, 75–77, 82, 87, 89, 107, 108, 111–113, 116, 118, 119, 122, 123, 125, 128, 130–132, 134–137, 139], as thoroughly discussed in previous sections. In the following, we provide a brief summary of the main conclusions with respect to key demographic, socioeconomic, and behavioural factors as these may be gleaned from reviews carried out within the past two decades.

4.9.1 Age

Gingivitis Burt [41] observed that gingivitis is found in early childhood, is more prevalent and severe in adolescence, and tends to level off in older age groups. Albandar [131] concluded that gingivitis is ubiquitous in populations of children and adults globally and found that the prevalence of gingival bleeding is fairly constant with age in North America [135]. Similarly, age did not influence the extent of gingivitis among adults from Southern Brazil [119].

Periodontitis The 'effect' of age seems to be different for periodontitis measures based on pocket depth and for periodontitis measures based on clinical attachment level. Hence, while periodontitis measures based on clinical attachment level show that periodontitis prevalence increases with increasing age [124, 130, 134], conclusions from periodontitis measures based on pocket depth indicate a fairly constant occurrence with age. However, one review has indicated that the prevalence of increased probing depth also increases with age [135].

Burt [41] found that the prevalence and severity of CAL is invariably related directly to age in cross-sectional surveys, an observation also made by Albandar [131], and expanded to cover prevalence, extent, and severity by Albandar [134]. Eke et al. [140] found a higher prevalence of periodontitis among 75+-yr-olds compared with 65–74-yr-olds. Overall, the prevalence and extent of destructive periodontal disease among Latin American adults increase with increased age [119], a conclusion seconded by the observation that periodontitis is more prevalent among the older age groups [120]. Susin et al. [75] found that aggressive periodontitis is detected more frequently among older children and young adults than in younger children. A systematic review by Needleman et al. [82] found '*surprisingly little effect'* of age on periodontitis progression assessed using the mean annual attachment level change.

The above conclusions regarding the associations with age are somewhat contradicted by the observations made in a much-cited global systematic review and meta-regression attempting to estimate the global burden of severe periodontitis [109, 111]. It was found that the prevalence of severe periodontitis, measured as either CPITN code 4 (PD ≥ 6 mm), CAL > 6 mm, or PD > 5 mm, increases with age until age 40, after which age the prevalence remains stable [109, 111]. This pattern resulted from a steep increase in the incidence rate for severe periodontitis from the age of about 20 year, which peaked around age 38 year, and showed a steep decline during the fifth decade of life to relatively low levels, which would remain fairly constant thereafter. However, in view of the different age profiles for periodontitis generated by epidemiologic data based on pocket depth and data based on clinical attachment level, it is difficult to interpret the results of this meta-regression study.

4.9.2 Gender

Gingivitis Gender did not influence the extent of gingivitis among adults from Southern Brazil [119], whereas Albandar [135] reported more gingivitis in males than in females. Burt [41] found that the extent of gingivitis was higher in older than in younger males, whereas this contrast was not seen among women. The prevalence of BOP did not differ according to sex among elderly Chinese [113].

Periodontitis It is almost unanimously agreed that men fare worse than women in terms of the prevalence, extent, and severity of periodontitis. Both Burt [41] and Albandar [131, 134] concluded that CAL of all levels of severity is generally more prevalent in males than in females. Yang et al. [107] found that the prevalence of both PD ≥ 4 mm and CAL ≥ 4 mm was higher among elderly Chinese men than among women. Similarly, Eke et al. [140] found a higher prevalence of periodontitis among elderly men than among elderly women. Corbet and Leung [122] found that periodontal diseases are more prevalent in men than in women throughout the Asian region. Based on a systematic review dedicated to the gender difference question, Shiau and Reynolds [113] concluded that the prevalence of destructive periodontal disease is higher in men than in women, whereas the rate of progression was similar for men and women. This concurs with the observation in the systematic review by Needleman et al. [82] that *'surprisingly little effect'* of gender was found on the mean annual attachment loss (i.e. periodontitis progression).

Diverging conclusions regarding the effect of gender on periodontitis have been expressed by Susin et al. [75] who found that some studies indicate no effect of gender on the prevalence of aggressive periodontitis, while other studies have reported gender contrasts, though not in the same direction. This led to the proposal that this association is likely to be influenced by other demographic characteristics, such as race/ethnicity [75]. Moreover, the results of the aforementioned global systematic review and meta-regression attempting to estimate the global burden of severe periodontitis [109, 111] once again deviate in their conclusion that the age-standardized prevalence and incidence estimates for severe periodontitis were similar for men and women.

4.9.3 Race/Ethnicity

Susin et al. [75] reported that aggressive periodontitis is detected more frequently among people of African origin than among people of Hispanic or Asian origin, while Caucasians have the lowest prevalence. Albandar [131] also noted similar differences in the prevalence estimates for chronic periodontitis among children and adolescents and among adult groups [134], with the lowest estimates concerning Caucasians followed by Asians, Hispanics and Latin Americans, and Africans and African Americans. Albandar and Tinoco [136] found a low level of periodontitis among children and young adult Caucasians in Western Europe and North America and much higher prevalence rates in young populations of other ethnicities.

4.9.4 Country/Region

It is widely agreed that the prevalence, extent, severity, and progression of periodontitis show considerable variation across the World's major regions, countries, and even across regions within countries. Kassebaum et al. [111] found considerable variation in the prevalence and incidence of severe periodontitis between World regions and countries. Albandar [131] noted that young Caucasians in Western Europe and North America have low frequencies of chronic periodontitis, while relatively high frequencies have been reported for Africa and Latin America. Similar observations were noted by Albandar and Tinoco [136]. Botero et al. [118] found that the overall prevalence of gingivitis among Latin American children was 35%, highest in Bolivia (73%) and Colombia (77%), and lowest in Mexico (23%). The prevalence of moderate to severe periodontal attachment loss is high, but the extent is low among adult populations in Latin America and possibly lower than seen in Asia and Africa [119]. König et al. [77] found that the epidemiologic data on periodontitis among European countries showed a fragmentary picture, with Spain, Sweden, and Switzerland being the healthier and Germany the more disease prone European countries. Eke et al. [140] found considerable interstate variation in the prevalence of periodontitis among the elderly population, with the South and Southwestern states displaying the higher prevalence estimates. Needleman et al. [82] found that the mean annual attachment loss was about three times higher in Sri Lanka and China than in North America and Europe. Thomson [89] found that longitudinal studies suggested a higher periodontitis progression rate among older people in developing countries than in developed ones.

4.9.5 Socioeconomic Factors

Burt [41] found that the occurrence of gingivitis is clearly related to lower socioeconomic status, while the relationship between periodontitis and socioeconomic status was less direct. However, subsequent reviews have been rather unanimous in their report of an association between socioeconomic factors and the epidemiologic estimates of periodontitis. Eke et al. [140] reported an inverse relationship between income and periodontitis prevalence among elderly Americans. Low socioeconomic status was found to be a risk factor for gingivitis among Latin-American children and adolescents [118]. Borrell and Crawford [121] observed that persons who are socioeconomically disadvantaged have poorer periodontal outcomes, regardless of the socioeconomic position indicator used. Borrell and Papapanou [130] found that socioeconomic indicators, such as education and income, are robust markers of periodontitis occurrence. Albandar [131, 134] found that low socioeconomic status groups have a higher occurrence of attachment loss and probing depth than those of high socioeconomic status. Schuch et al. [110] reported that a relatively low socioeconomic position earlier in life, as indicated by education, occupation or income, is associated with poorer periodontal health later in life.

4.9.6 Behavioural Factors

Smoking Burt [41] found that smoking is clearly a risk for periodontitis, while smoking exerts a masking effect on the signs of inflammation, including gingivitis measured by BOP. Eke et al. [140] reported that elderly American smokers had a markedly higher prevalence of periodontitis, including severe periodontitis, than former or never smokers. Borrell and Papananou [130] found strong evidence for an association between smoking and the prevalence and severity of periodontitis, and the observations of Albandar [131, 134] support this conclusion. Heitz-Mayfield [129] concluded that cigarette smoking represents a risk factor for periodontitis progression, and noted that the effect may be dose related.

Oral Hygiene Burt [41] found that the relationship of oral hygiene to periodontitis is less straightforward. However, Lertpimonchai et al. [108] found that people whose oral hygiene was characterized as poor had an odds ratio of 5 for periodontitis compared to people whose oral hygiene was considered good, and the odds ratio for periodontitis with fair oral hygiene was 2.0.

Poor oral hygiene was found to be a risk factor for gingivitis among Latin-American children and adolescents [118]. Infrequent toothbrushing has been found to be associated with severe periodontitis [112].

4.9.7 Trends in Periodontal Diseases over Time

Burt [41] noted an improvement in gingival health from the mid-1960s to the 1990s. Hugoson and Norderyd [125] found indications of a possible trend for a lower prevalence of both gingivitis and periodontitis, though the latter would seem mainly comprising mild-moderate periodontitis. Cobb et al. [124] concluded that the data available from the USA suggest a progressive decline in the prevalence of moderate-to-advanced periodontitis. López et al. [115] noted that the prevalence and extent of CAL had decreased among seniors aged 65+ in both the USA and in Germany over a period of about 10 years. Holtfreter et al. [116] reviewed the evidence for a decline in periodontitis prevalence and found that the

evidence supported a trend for decline, despite methodological issues hampering interpretability of the trend studies. Once again, the systematic review and metaregression by Kassebaum et al. [109, 111] delivers the contradicting conclusion, by indicating that the global age-standardized prevalence of severe periodontitis has remained stable at 10.8% between 1990 and 2010.

Point of Emphasis

Numerous reviews have been undertaken of factors influencing gingivitis and periodontitis epidemiology, and most express concerns about the distorting effects of considerable variability in methodology and quality of the original studies.

4.10 The Way Forward in Periodontal Epidemiology?

In the above account, we have tried to paint an overall picture of the key epidemiological features of periodontal disease, as these emerge from reviews carried out during the past two decades. However, despite the many attempts to provide firm evidence through systematic or narrative reviews, one must conclude that the evidence gets no better than the basic studies included. Attempts to provide 'global' overviews of the distribution of prevalence, extent, severity, rate of progression, and trends over time – not to mention the provision of 'global' estimates of these features – all face the problem of the insurmountably large variation in the methods used in the epidemiologic studies underlying the reviews. As long as sampling methods and participation rates differ, and recording methods and protocols, parameters used to define disease, and disease classifications are not universally agreed upon, such reviews are unlikely to provide accurate information. Add to this complexity the trends for change over time in tooth retention and gingival health among populations, and it should become clear that large odds work against valid conclusions from such global overviews of the epidemiologic evidence.

Fortunately, periodontal disease epidemiology is not a pollster's enterprise, and while public health professionals may indeed crave for statistically valid estimates of disease occurrence at a specific time in a given population, it is also clear that such estimates are no more than sampling snapshots [141]. We should acknowledge that 'representativeness is gone as we speak' [142], because it is time and place specific and therefore inherently a historical concept. Already Heraclitus (~ 500 BC) knew this when he noted that *'you could not step twice into the same river'* [143]. The issue of generalization of the results of an epidemiological study to wider populations goes beyond considerations of representativeness in the statistical sense. Not only are the goals of scientific and statistical inference rather different; they also build on very different sets of logic that must be distinguished [142]. Representativeness is relevant where the inferential process is purely statistical, rather than scientific. Scientific inference, however, is a process that involves moving from the particulars of a given set of observations to the abstraction of a scientific theory, which is *'divorced from time and place'* [144], and the broader understanding of a phenomenon and the validity of a generalization is *'ultimately a matter of informed judgment'* [144].

We therefore find it more pertinent to glean our periodontal epidemiological information from the results of some large, regional, or even national epidemiological surveys [49, 55, 69, 140, 145–158] of periodontal diseases in populations, precisely because each of these larger studies offers internal methodological consistency and therefore internal validity. The generalization of their results to wider or different populations (including the ever-present group of non-participants/non-responders) would, in our view, depend on the assumptions made about the realms of the study results [78], and such are necessarily based on external information. A key question to address is whether – or to what extent – the determinants studied and the effects estimated are conceivably related to the non-representativeness of study participants, as it must be born in mind that the non-response rates observed even in probability sampled surveys are typically non-negligible and often considerable, ranging from 20% to 30% [69, 159] to more than 50% [155, 157]. While external data might be available that would allow us to explore the possible impact of non-participation on our study results, for example, by propensity scoring [160–162], conclusions would always be conditioned on the information being incomplete and therefore invariably involve some degree of extrapolation.

Conclusion The study of periodontal disease epidemiology within and across populations is greatly hampered by the lack of a commonly accepted and clinically operational definition of periodontitis and the huge variation in the methods used in periodontal disease epidemiological studies. Even so, it may be concluded that the distribution of the parameters of periodontitis within a population show a pronounced right skewness, such that the majority presents only mild and localized signs of periodontal destruction, whereas a smaller proportion presents with destruction of an extent and severity that may endanger tooth retention. Higher age, male gender, low socioeconomic position, and smoking are the sociodemographic and behavioural factors that most consistently have been reported to be positively associated with higher prevalence, extent, and severity of periodontitis.

References

1. MacMahon B, Trichopoulos D. Principles of epidemiology. Boston: Little, Brown & Co.; 1996.
2. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14:32–8.
3. Scherp HW. Current concepts in periodontal disease research: epidemiological contributions. J Am Dent Assoc. 1964;68: 667–75.
4. Savage A, Eaton KA, Moles DR, Needleman I. A systematic review of definitions of periodontitis and methods that have been used to identify this disease. J Clin Periodontol. 2009;36:458–67.
5. Preshaw PM. Definitions of periodontal disease in research. J Clin Periodontol. 2009;36:1–2.
6. López R, Baelum V. Contesting conventional periodontal wisdom: implications for periodontal classifications. Community Dent Oral Epidemiol. 2012;40:385–95.
7. American Academy of Periodontology. Proceedings of the World Workshop in Clinical Periodontics. Princeton, New Jersey, July 23–27, 1989. Consensus report. Discussion section I. Periodontal diagnosis and diagnostic aids. Chicago: American Academy of Periodontology; 1989.
8. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999;4:1–6.
9. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89(Suppl 1):S173–S82.
10. López R, Baelum V. Periodontal disease classifications revisited. Eur J Oral Sci. 2015;123:385–9.
11. Costa FO, Guimaraes AN, Cota LO, Pataro AL, Segundo TK, Cortelli SC, et al. Impact of different periodontitis case definitions on periodontal research. J Oral Sci. 2009;51:199–206.
12. Baelum V, Lopez R. Defining a periodontitis case: analysis of a never-treated adult population. J Clin Periodontol. 2012;39: 10–9.
13. Lopez R, Baelum V. Classifying periodontitis among adolescents: implications for epidemiological research. Community Dent Oral Epidemiol. 2003;31:136–43.
14. Kongstad J, Enevold C, Christensen LB, Fiehn NE, Holmstrup P. Impact of periodontitis case criteria: a cross-sectional study of lifestyle. J Periodontol. 2017;88:602–9.
15. van der Velden U. Letter to the editor. Diagnosis of periodontitis. J Clin Periodontol. 2000;27:960–1.
16. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Periodontol. 2018;89 Suppl 1: S159–S72.
17. Baelum V, Lopez R. Defining and classifying periodontitis: need for a paradigm shift? Eur J Oral Sci. 2003;111:2–6.
18. Ranney RR. Diagnosis of periodontal diseases. Adv Dent Res. 1991;5:21–36.
19. Moore WEC, Moore LH, Ranney RR, Smibert RM, Burmeister JA, Schenkein HA. The microflora of periodontal sites showing active destructive progression. J Clin Periodontol. 1991;18: 729–39.
20. Lang N, Bartold PM, Cullinan M, Jeffcoat M, Mombelli A, Murakami S, et al. Consensus report. Aggressive periodontitis. Ann Periodontol. 1999;4:53.
21. Leroy R, Eaton KA, Savage A. Methodological issues in epidemiological studies of periodontitis - how can it be improved? BMC Oral Health. 2010;10:8.
22. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Periodontol. 2018;89:S1–8.
23. Chapple ILC, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89 Suppl 1:S74–84.
24. Trombelli L, Farina R, Silva CO, Tatakis DN. Plaque-induced gingivitis: case definition and diagnostic considerations. J Periodontol. 2018;89 Suppl 1:S46–73.
25. Armitage GC. Periodontal diagnoses and classification of periodontal diseases. Periodontol 2000. 2004;34:9–21.
26. Wulff HR. What is understood by a disease entity? J Royal Coll Phys London. 1979;13:219–20.
27. Scadding JG. Essentialism and nominalism in medicine: logic of diagnosis in disease terminology. Lancet. 1996;348:594–6.
28. Scadding JG. Diagnosis: the clinician and the computer. Lancet. 1967;2:877–82.
29. Campbell EJM, Scadding JG, Roberts RS. The concept of disease. BMJ. 1979;2(6193):757–62.
30. Baelum V, Manji F, Fejerskov O. The distribution of periodontal destruction in the populations of non-industrialized countries: evidence for the existence of high risk groups and individuals. In: Johnson NW, editor. Risk markers for oral diseases. Periodontal diseases. Markers of disease susceptibility and activity. Cambridge: Cambridge University Press; 1991. p. 27–75.
31. Papapanou PN. The prevalence of periodontitis in the US: forget what you were told. J Dent Res. 2012;91:907–8.
32. Papapanou PN, Susin C. Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both? Periodontol 2000. 2017;75:45–51.
33. Lang NP, Bartold PM. Periodontal health. J Periodontol. 2018;89(Suppl 1):S9–S16.
34. Marshall-Day CD, Stephens RG, Quigley LF. Periodontal disease: prevalence and incidence. J Periodontol. 1955;26:185–203.
35. Russell AL. A system of classification and scoring for prevalence surveys of periodontal disease. J Dent Res. 1956;35:350–9.
36. Ramfjord SP. Indices for prevalence and incidence of periodontal disease. J Periodontol. 1959;30:51–9.
37. Johansen JR, Gjermo P, Bellini HT. A system to classify the need for periodontal treatment. Acta Odontol Scand. 1973;31:297–305.
38. Ainamo J, Barmes D, Beagrie G, Cutress T, Martin J. Development of the World Health Organization (WHO) Community Periodontal Index of Treatment Needs (CPITN). Int Dent J. 1982;32:281–91.
39. World Health Organization. Oral health surveys. Basic methods. 4th ed. Geneva: World Health Organization; 1997.
40. World Health Organization. Oral health surveys. Basic methods. 5th ed. Geneva: World Health Organization; 2013.
41. Burt B, on behalf of the Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: epidemiology of periodontal diseases. J Periodontol. 2005;76:1406–19.
42. Baelum V, Lopez R. Periodontal disease epidemiology - learned and unlearned? Periodontol 2000. 2013;62:37–58.
43. Baelum V, Lopez R. Periodontal epidemiology: towards social science or molecular biology? Community Dent Oral Epidemiol. 2004;32:239–49.
44. Goodson JM, Tanner ACR, Haffajee AD, Sornberger GC, Socransky SS. Patterns of progression and regression of destructive periodontal disease. J Clin Periodontol. 1982;9:472–81.

45. Cutress TW, Powell RN, Ball ME. Differing profiles of periodontal disease in two similar South Pacific island populations. Community Dent Oral Epidemiol. 1982;10:193–203.
46. Blicher B, Joshipura K, Eke P. Validation of self-reported periodontal disease: a systematic review. J Dent Res. 2005;84: 881–90.
47. Lang NP, Adler R, Joss A, Nyman S. Absence of bleeding of probing. An indicator of periodontal stability. J Clin Periodontol. 1990;17:714–21.
48. Joss A, Adler R, Lang NP. Bleeding on probing. A parameter for monitoring periodontal conditions in clinical practice. J Clin Periodontol. 1994;21:402–8.
49. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ, on behalf of the the participating members of the CDC Periodontal Disease Surveillance workgroup. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res. 2012;91:914–20.
50. Baelum V, Fejerskov O, Manji F. Periodontal diseases in adult Kenyans. J Clin Periodontol. 1988;15:445–52.
51. Lang NP, Tonetti MS. Periodontal diagnosis in treated periodontitis. Why, when and how to use clinical parameters. J Clin Periodontol. 1996;23:240–50.
52. Lopez R, Frydenberg M, Baelum V. Clinical features of early periodontitis. J Periodontol. 2009;80:749–58.
53. Lopez R, Fernandez O, Jara G, Baelum V. Epidemiology of clinical attachment loss in adolescents. J Periodontol. 2001; 72:1666–74.
54. Corraini P, Baelum V, Lopez R. Reliability of direct and indirect clinical attachment level measurements. J Clin Periodontol. 2013;40:896–905.
55. Billings M, Holtfreter B, Papapanou PN, Mitnik GL, Kocher T, Dye BA. Age-dependent distribution of periodontitis in two countries: findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012. J Periodontol. 2018;89 Suppl 1: S140–S58.
56. American Academy of Periodontology Task Force report on the update to the 1999 classification of periodontal diseases and conditions. J Periodontol. 2015;86:835–8.
57. Hujoel PP, Aps JK, Bollen AM. What are the cancer risks from dental computed tomography? J Dent Res. 2015;94:7–9.
58. Baelum V, Luan WM, Chen X, Fejerskov O. A 10-year study of the progression of destructive periodontal disease in adult and elderly Chinese. J Periodontol. 1997;68:1033–42.
59. Baelum V, Luan WM, Chen X, Fejerskov O. Predictors of destructive periodontal disease incidence and progression in adult and elderly Chinese. Community Dent Oral Epidemiol. 1997;25:265–72.
60. Baelum V, Luan WM, Fejerskov O, Chen X. Tooth mortality and periodontal conditions in 60-80-year-old Chinese. Scand J Dent Res. 1988;96:99–107.
61. Yoneyama T, Okamoto H, Lindhe J, Socransky SS, Haffajee AD. Probing depth, attachment loss and gingival recession. Findings from a clinical examination in Ushiku, Japan. J Clin Periodontol. 1988;15:581–91.
62. Okamoto H, Yoneyama T, Lindhe J, Haffajee A, Socransky S. Methods of evaluating periodontal disease data in epidemiological research. J Clin Periodontol. 1988;15:430–9.
63. Beltran-Aguilar ED, Eke PI, Thornton-Evans G, Petersen PE. Recording and surveillance systems for periodontal diseases. Periodontol 2000. 2012;60:40–53.
64. Holtfreter B, Albandar JM, Dietrich T, Dye BA, Eaton KA, Eke PI, et al. Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: proposed standards from the Joint EU/USA Periodontal Epidemiology Working Group. J Clin Periodontol. 2015;42: 407–12.
65. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. J Periodontol. 2012;83(12):1449–54.
66. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol. 2007;78:1387–99.
67. Baelum V, Chen X, Manji F, Luan WM, Fejerskov O. Profiles of destructive periodontal disease in different populations. J Periodontal Res. 1996;31:17–26.
68. Holtfreter B, Schwahn C, Biffar R, Kocher T. Epidemiology of periodontal diseases in the study of health in Pomerania. J Clin Periodontol. 2009;36:114–23.
69. Holtfreter B, Demmer RT, Bernhardt O, Papapanou PN, Schwahn C, Kocher T, et al. A comparison of periodontal status in the two regional, population-based studies of SHIP and INVEST. J Clin Periodontol. 2012;39:1115–24.
70. Meisel P, Kocher T. Definitions of periodontal disease in research: an alternative view. J Clin Periodontol. 2009;36: 411–2.
71. Beck JD, Koch GG, Rozier RG, Tudor GE. Prevalence and risk indicators for periodontal attachment loss in a population of older community-dwelling blacks and whites. J Periodontol. 1990;61:521–8.
72. Brown LJ, Oliver RC, Løe H. Evaluating periodontal status of US employed adults. J Am Dent Assoc. 1990;121:226–32.
73. Tonetti MS, Claffey N. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. J Clin Periodontol. 2005;32 Suppl 6:210–3.
74. Eke PI, Thornton-Evans G, Dye B, Genco R. Advances in surveillance of periodontitis: The Centers for Disease Control and Prevention Periodontal Disease Surveillance Project. J Periodontol. 2012;83:1337–42.
75. Susin C, Haas AN, Albandar JM. Epidemiology and demographics of aggressive periodontitis. Periodontol 2000. 2014; 65:27–45.
76. Baelum V, Scheutz F. Periodontal diseases in Africa. Periodontol 2000. 2002;29:79–103.
77. Konig J, Holtfreter B, Kocher T. Periodontal health in Europe: future trends based on treatment needs and the provision of periodontal services - position paper 1. Eur J Dent Educ. 2010;14 Suppl 1:4–24.
78. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. In: Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008. p. 128–47.
79. Tran DT, Gay I, Du XL, Fu Y, Bebermeyer RD, Neumann AS, et al. Assessing periodontitis in populations: a systematic review of the validity of partial-mouth examination protocols. J Clin Periodontol. 2013;40:1064–71.
80. Holtfreter B, Alte D, Schwahn C, Desvarieux M, Kocher T. Effects of different manual periodontal probes on periodontal measurements. J Clin Periodontol. 2012;39:1032–41.
81. Rothman KJ, Greenland S, Poole C, Lash TL. Causation and causal inference. In: Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 5–31.
82. Needleman I, Garcia R, Gkranias N, Kirkwood KL, Kocher T, Iorio AD, et al. Mean annual attachment, bone level, and tooth loss: a systematic review. J Periodontol. 2018;89 Suppl 1: S120–S39.
83. Susin C, Kingman A, Albandar JM. Effect of partial recording protocols on estimates of prevalence of periodontal disease. J Periodontol. 2005;76:262–7.
84. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA. Accuracy of NHANES periodontal examination protocols. J Dent Res. 2010;89:1208–13.

85. Kingman A, Susin C, Albandar JM. Effect of partial recording protocols on severity estimates of periodontal disease. J Clin Periodontol. 2008;35:659–67.
86. Albandar JM. Underestimation of periodontitis in NHANES surveys. J Periodontol. 2011;82:337–41.
87. Merchant AT, Pitiphat W. Researching periodontitis: challenges and opportunities. J Clin Periodontol. 2007;34:1007–15.
88. Manji F, Baelum V, Fejerskov O. Tooth mortality in an adult rural population in Kenya. J Dent Res. 1988;67:496–500.
89. Thomson WM. Epidemiology of oral health conditions in older people. Gerodontol. 2014;31:9–16.
90. Haworth S, Shungin D, Kwak SY, Kim HY, West NX, Thomas SJ, et al. Tooth loss is a complex measure of oral disease: determinants and methodological considerations. Community Dent Oral Epidemiol. 2018;46:555–62.
91. Priest G. Revisiting tooth preservation in prosthodontic therapy. J Prosthodont. 2011;20:144–52.
92. Kao RT. Strategic extraction: a paradigm shift that is changing our profession. J Periodontol. 2008;79:971–7.
93. Zitzmann NU, Krastl G, Hecker H, Walter C, Waltimo T, Weiger R. Strategic considerations in treatment planning: deciding when to treat, extract, or replace a questionable tooth. J Prosthet Dent. 2010;104:80–91.
94. Bader JD, Shugars DA. Variation in dentists' clinical decisions. J Public Health Dent. 1995;55:181–8.
95. Gilbert GH, Shelton BJ, Chavers LS, Bradford EH Jr. Predicting tooth loss during a population-based study: role of attachment level in the presence of other dental conditions. J Periodontol. 2002;73:1427–36.
96. Baelum V, van Palenstein HW, Hugoson A, Yee R, Fejerskov O. A global perspective on changes in the burden of caries and periodontitis: implications for dentistry. J Oral Rehabil. 2007;34:872–906.
97. Hugoson A, Sjödin B, Norderyd O. Trends over 30 years, 1973-2003, in the prevalence and severity of periodontal disease. J Clin Periodontol. 2008;35:405–14.
98. Wahlin A, Papias A, Jansson H, Norderyd O. Secular trends over 40 years of periodontal health and disease in individuals aged 20–80 years in Jonkoping, Sweden: repeated cross-sectional studies. J Clin Periodontol. 2018;45:1016–24.
99. Hugoson A, Norderyd O, Slotte C, Thorstensson H. Distribution of periodontal disease in a Swedish adult population 1973, 1983 and 1993. J Clin Periodontol. 1998;25:542–8.
100. Norderyd O, Koch G, Papias A, Kohler AA, Helkimo AN, Brahm CO, et al. Oral health of individuals aged 3-80 years in Jonkoping, Sweden during 40 years (1973-2013). II. Review of clinical and radiographic findings. Swed Dent J. 2015;39:69–86.
101. Robinson PJ, Vitek RM. The relationship between gingival inflammation and resistance to probe penetration. J Periodont Res. 1979;14:239–43.
102. Larsen C, Barendregt DS, Slot DE, Van der Velden U, Van der Weijden F. Probing pressure, a highly undervalued unit of measure in periodontal probing: a systematic review on its effect on probing pocket depth. J Clin Periodontol. 2009;36:315–22.
103. Hefti AF. Periodontal probing. Crit Rev Oral Biol Med. 1997;8:336–56.
104. Garnick JJ, Silverstein L. Periodontal probing: probe tip diameter. J Periodontol. 2000;71:96–103.
105. Greenstein G. Contemporary interpretation of probing depth assessments: diagnostic and therapeutic implications. A literature review. J Periodontol. 1997;68:1194–205.
106. Elashiry M, Meghil MM, Arce RM, Cutler CW. From manual periodontal probing to digital 3-D imaging to endoscopic capillaroscopy: recent advances in periodontal disease diagnosis. J Periodontal Res. 2019; 54(1):1–9.
107. Yang H, Xiao L, Zhang L, Deepal S, Ye G, Zhang X. Epidemic trend of periodontal disease in elderly Chinese population, 1987-2015: a systematic review and meta-analysis. Sci Rep. 2017;7. https://doi.org/10.1038/srep45000.
108. Lertpimonchai A, Rattanasiri S, Arj-Ong Vallibhakara S, Attia J, Thakkinstian A. The association between oral hygiene and periodontitis: a systematic review and meta-analysis. Int Dent J. 2017;67:332–43.
109. Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T. Global epidemiology of dental caries and severe periodontitis - a comprehensive review. J Clin Periodontol. 2017;44 Suppl 18:S94–S105.
110. Schuch HS, Peres KG, Singh A, Peres MA, Do LG. Socioeconomic position during life and periodontitis in adulthood: a systematic review. Community Dent Oral Epidemiol. 2017;45:201–8.
111. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res. 2014;93:1045–53.
112. Zimmermann H, Zimmermann N, Hagenfeld D, Veile A, Kim TS, Becher H. Is frequency of tooth brushing a risk factor for periodontitis? A systematic review and meta-analysis. Community Dent Oral Epidemiol. 2015;43:116–27.
113. Shiau HJ, Reynolds MA. Sex differences in destructive periodontal disease: a systematic review. J Periodontol. 2010;81:1379–89.
114. Hujoel PP, Lingstrom P. Nutrition, dental caries and periodontal disease: a narrative review. J Clin Periodontol. 2017;44 Suppl 18:S79–84.
115. Lopez R, Smith PC, Gostemeyer G, Schwendicke F. Ageing, dental caries and periodontal diseases. J Clin Periodontol. 2017;44 Suppl 18:S145–S52.
116. Holtfreter B, Schützhold S, Kocher T. Is periodontitis prevalence declining? A review of the current literature. Curr Oral Health Rep. 2014;1:251–61.
117. Chandra A, Yadav OP, Narula S, Dutta A. Epidemiology of periodontal diseases in Indian population since last decade. J Int Soc Prev Community Dent. 2016;6:91–6.
118. Botero JE, Rosing CK, Duque A, Jaramillo A, Contreras A. Periodontal disease in children and adolescents of Latin America. Periodontol 2000. 2015;67:34–57.
119. Oppermann RV, Haas AN, Rosing CK, Susin C. Epidemiology of periodontal diseases in adults from Latin America. Periodontol 2000. 2015;67:13–33.
120. Al-Harthi LS, Cullinan MP, Leichter JW, Thomson WM. Periodontitis among adult populations in the Arab World. Int Dent J. 2013;63:7–11.
121. Borrell LN, Crawford ND. Socioeconomic position indicators and periodontitis: examining the evidence. Periodontol 2000. 2012;58:69–83.
122. Corbet EF, Leung WK. Epidemiology of periodontitis in the Asia and Oceania regions. Periodontol 2000. 2011;56:25–64.
123. Demmer RT, Papapanou PN. Epidemiologic patterns of chronic and aggressive periodontitis. Periodontol 2000. 2010;53:28–44.
124. Cobb CM, Williams KB, Gerkovitch MM. Is the prevalence of periodontitis in the USA in decline? Periodontol 2000. 2009;50:13–24.
125. Hugoson A, Norderyd O. Has the prevalence of periodontitis changed during the last 30 years? J Clin Periodontol. 2008;35:338–45.
126. Corbet EF. Periodontal diseases in Asians. J Int Acad Periodontol. 2006;8:136–44.
127. Persson GR. What has ageing to do with periodontal health and disease? Int Dent J. 2006;56:240–9.

128. Gjermo PE. Impact of periodontal preventive programmes on the data from epidemiologic studies. J Clin Periodontol. 2005;32 Suppl 6:294–300.
129. Heitz-Mayfield LJ. Disease progression: identification of high-risk groups and individuals for periodontitis. J Clin Periodontol. 2005;32 Suppl 6:196–209.
130. Borrell LN, Papapanou PN. Analytic epidemiology of periodontitis. J Clin Periodontol. 2005;32 Suppl 6:132–58.
131. Albandar JM. Epidemiology and risk factors of periodontal diseases. Dent Clin N Am. 2005;49:517–32, v–vi.
132. Irfan UM, Dawson DV, Bissada NF. Epidemiology of periodontal disease: a review and clinical perspectives. J Int Acad Periodontol. 2001;3:14–21.
133. Albandar JM, Rams TE. Risk factors for periodontitis in children and young persons. Periodontol 2000. 2002;29:207–22.
134. Albandar JM. Global risk factors and risk indicators for periodontal diseases. Periodontol 2000. 2002;29:177–206.
135. Albandar JM. Periodontal diseases in North America. Periodontol 2000. 2002;29:31–69.
136. Albandar JM, Tinoco EMB. Global epidemiology of periodontal diseases in children and young persons. Periodontol 2000. 2002;29:153–76.
137. Corbet EF, Zee KY, Lo EC. Periodontal diseases in Asia and Oceania. Periodontol 2000. 2002;29:122–52.
138. Sheiham A, Netuveli GS. Periodontal diseases in Europe. Periodontol 2000. 2002;29:104–21.
139. Jenkins WMM, Papapanou PN. Epidemiology of periodontal disease in children and adolescents. Periodontol 2000. 2001;26:16–32.
140. Eke PI, Wei L, Borgnakke WS, Thornton-Evans G, Zhang X, Lu H, et al. Periodontitis prevalence in adults >/= 65 years of age, in the USA. Periodontol 2000. 2016;72:76–95.
141. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. Int J Epidemiol. 2013;42:1012–4.
142. Nohr EA, Olsen J. Commentary: epidemiologists have debated representativeness for more than 40 years - has the time come to move on? Int J Epidemiol. 2013;42:1016–7.
143. Stanford Encyclopedia of Philosophy [Accessed January 25, 2019]. Available from: https://plato.stanford.edu/entries/heraclitus/.
144. Rothman KJ. Modern epidemiology. Boston: Little, Brown and Company; 1986. p. 77–97.
145. Slade GD, Spencer AJ, Roberts-Thomson KF. Australia's dental generations. The national survey of adult oral health 2004-06. Canberra; 2007. Contract No.: AIHW cat. no. DEN 165.
146. Kocher T, Schwahn C, Gesch D, Bernhardt O, John U, Meisel P, et al. Risk determinants of periodontal disease - an analysis of the Study of Health in Pomerania (SHIP 0). J Clin Periodontol. 2005;32:59–67.
147. Gatke D, Holtfreter B, Biffar R, Kocher T. Five-year change of periodontal diseases in the Study of Health in Pomerania (SHIP). J Clin Periodontol. 2012;39:357–67.
148. Dye BA, Li X, Lewis BG, Iafolla T, Beltran-Aguilar ED, Eke PI. Overview and quality assurance for the oral health component of the National Health and Nutrition Examination Survey (NHANES), 2009–2010. J Public Health Dent. 2014;74:248–56.
149. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. J Periodontol. 2015;86:611–22.
150. Schutzhold S, Kocher T, Biffar R, Hoffmann T, Schmidt CO, Micheelis W, et al. Changes in prevalence of periodontitis in two German population-based studies. J Clin Periodontol. 2015;42:121–30.
151. Eke PI, Zhang X, Lu H, Wei L, Thornton-Evans G, Greenlund KJ, et al. Predicting periodontitis at state and local levels in the United States. J Dent Res. 2016;95:515–22.
152. Eke PI, Wei L, Thornton-Evans GO, Borrell LN, Borgnakke WS, Dye B, et al. Risk indicators for periodontitis in US adults: NHANES 2009 to 2012. J Periodontol. 2016;87:1174–85.
153. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US adults: National health and nutrition examination survey 2009–2014. J Am Dent Assoc. 2018;149:576–88.. e6
154. Eke PI, Lu H, Zhang X, Thornton-Evans G, Borgnakke WS, Holt JB, et al. Geospatial distribution of periodontists and US adults with severe periodontitis. J Am Dent Assoc. 2019;150(2):103–110.
155. White DA, Tsakos G, Pitts NB, Fuller E, Douglas GV, Murray JJ, et al. Adult Dental Health Survey 2009: common oral health conditions and their impact on the population. Br Dent J. 2012;213:567–72.
156. Chung SY, Song KB, Lee SG, Choi YH. The strength of age effect on tooth loss and periodontal condition in Korean elderly. Arch Gerontol Geriatr. 2011;53:e243–8.
157. Lorenzo SM, Alvarez R, Andrade E, Piccardo V, Francia A, Massa F, et al. Periodontal conditions and associated factors among adults and the elderly: findings from the first National Oral Health Survey in Uruguay. Cad Saude Publica. 2015;31:2425–36.
158. Carasol M, Llodra JC, Fernandez-Meseguer A, Bravo M, Garcia-Margallo MT, Calvo-Bonacho E, et al. Periodontal conditions among employed adults in Spain. J Clin Periodontol. 2016;43:548–56.
159. National Center for Health Statistics. National Health and Nutrition Examination Survey - NHANES response rates and population totals. CDC Centers for Disease Control and Prevention. Available from: https://wwwn.cdc.gov/nchs/nhanes/ResponseRates.aspx. Accessed 28 Jan 2019.
160. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc. 1984;79:516–24.
161. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.
162. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399–424.

Malocclusions

Karen Glazer Peres, Paulo Frazão, and Carlos Flores-Mir

Contents

5.1 Introduction – 80

5.2 Classification – 80
5.2.1 Malocclusion Classification – 80
5.2.2 Malocclusion Classification in Clinical Settings – 80
5.2.3 Malocclusion Classification in Epidemiological Settings – 81
5.2.4 Summary – 83

5.3 Epidemiology – 83
5.3.1 Deciduous Dentition – 83
5.3.2 Mixed Dentition – 87
5.3.3 Permanent Dentition – 90

5.4 Protective Factors and Risk Indicators for Malocclusions – 90
5.4.1 Socioeconomic Conditions – 90
5.4.2 Anthropometric Characteristics – 94
5.4.3 Child Behavior – 94
5.4.4 Maternal Characteristics – 95
5.4.5 Preventable Diseases and Conditions Associated with Malocclusion – 96

5.5 Impact of Malocclusion on Individuals' Quality of Life – 97

5.6 Final Considerations – 101

References – 101

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_5

5.1 Introduction

The formation, maturation, and continuous wearing of occlusal surfaces in deciduous, mixed, and permanent dentition are part of the same continuum series of events, the same phenomenon which undergoes constant change over time, whose components act on, interact, and condition each other in an individualized form. Thus, the occlusal characteristics and changes observed in these different dentition stages are part of a single process referred to as craniofacial growth and development [1]. For operational purposes, malocclusion is considered the misalignment of teeth and/or jaws that results from disorders in the dynamic process of craniofacial growth and development [2]. Misaligned teeth can cause a myriad of individual psychosocial problems related to impaired dentofacial aesthetics such as difficulties of social interaction or disturbances in oral functions, such as mastication, swallowing, and speech. This condition may also increase the susceptibility to dental trauma and accentuate periodontal disease or tooth decay risks related to malocclusion [3]. In addition, malocclusion may negatively affect oral health-related quality of life of any given individual. Poorer oral health–related quality of life has been associated with the presence of some types of malocclusion in individuals and populations from diverse socioeconomic backgrounds [4, 5] and at different stages of their life [6, 7]. Based on its potentially harmful effects and its high prevalence in different societies, malocclusion should be investigated and monitored as a public health problem. In this chapter, we describe alternatives to measure, classify, and investigate malocclusion from an epidemiological perspective. An overview of the frequency and the severity of malocclusion worldwide is also discussed, including its potential associated risk and protective factors. Finally, a review of studies which investigated the impact of malocclusion on oral health-related quality of life is depicted in tables.

5.2 Classification

5.2.1 Malocclusion Classification

Historically, there have been innumerable attempts to develop a comprehensive malocclusion classification system. To date, a universally acceptable one has not been identified. Reasons for this range from the differences in the occlusal factors to be assessed to the availability of adjunctive diagnostic tools in different settings like a private practice/hospital-based clinical setting to field conditions when assessing malocclusions for epidemiological purposes. For this reason, this section will assess the most used available classification systems in those two distinct settings. We will start with the description of approaches proposed for a clinical setting and we will finish with approaches for an epidemiological setting.

5.2.2 Malocclusion Classification in Clinical Settings

5.2.2.1 Angle's Malocclusion Classification

The oldest recognized malocclusion classification system was proposed by Edward H. Angle in 1890 [8]. This classification assumed that the nasomaxillary complex was set and immovable. Hence, any sagittal problem was originated by mandibular growth deficiency or excess. As no radiographic imaging was available, only the occlusion could have been used to assess malocclusion issues. In that sense, the upper first permanent molar was selected as the reference point and an analysis of the relative position of the lower first permanent molar in contrast to the upper first permanent molar was the basis of classification. Therefore, any relative forward molar position was considered a Class III malocclusion and any backward position as a Class II malocclusion. More specifically, all was about the relationship of the mesiobuccal cusp of the maxillary first permanent molar and the buccal groove of the mandibular first permanent molar.

When other occlusal factors were considered, both Class II and Class III malocclusions were further subdivided. In the case of the Class II malocclusion, it can be subdivided into a Division I (in addition to a Class II molar relationship, an increased OJ is noted), Division II (in addition to a Class II molar relationship, the maxillary centrals are retroclined and the maxillary laterals either proclined or normally inclined), and Subdivision (when only in one side, there is a Class II molar relationship, while in the other, there is a Class I molar relationship). In the case of the Class III malocclusion, it can be subdivided into a pseudo Class III (the Class III molar relationship is set by a postural sliding due to a occlusal interference) and Subdivision (when only in one side, there is a Class III molar relationship, while in the other, there is a Class I molar relationship).

Some strengths of this method are that it only requires clinical assessment and it is relatively easy to apply and communicate. Some drawbacks are that it does not consider transverse or vertical dimension as a source of the problem, a sagittal skeletal component is assumed, and it is not applicable to deciduous dentition.

5.2.2.2 Dewey's Modification

In 1915, Dewey [9] introduced a modification considering five types for Class I and three types for Class III malocclusions.

5.2.2.3 Simon's Classification

Back in 1930, Simon [10] proposed a classification system that was based on how dental arches were related to three anthropometric planes (Frankfort horizontal plane, orbital, and raphe median plane). Those planes all relatively perpendicular to the others allowed the analysis of the discrepancies in the three planes of space.

Some strengths of this method are that it considers all the 3D major components involved in a malocclusion, clear differentiation between dental and skeletal problems is made, and aesthetics is considered. Some drawbacks are that the etiology of the malocclusion is not considered and that it is based on a static analysis.

5.2.2.4 Ackermann and Proffit Classification

In 1969, these authors [11] proposed a modification from Angle's malocclusion classification to overcome some of its drawbacks. A Venn diagram was added to assess five malocclusion characteristics. Those are dentofacial appearance (symmetry, profile, lips, and incisor display), teeth/arch form considerations (alignment and symmetry), transversal, sagittal, and vertical analysis (skeletal and dental).

5.2.2.5 Andrew's Six Keys

In 1970, Lawrence Andrews [12] introduced six occlusal keys for defining an ideal occlusion. Those considered a correct molar relationship (Class I as defined by Angle), correct crown angulations and inclinations, no teeth rotations, no spacing between teeth, and almost flat Curve of Spee. In other words, he did not define different malocclusion types but only improved the detailing of what an ideal occlusion would be.

5.2.2.6 American Board of Orthodontics Discrepancy Index (ABO DI)

The American Board of Orthodontics Discrepancy Index (ABO DI) [13] was proposed in 2004 only to measure malocclusion complexity in individual cases, but lately, it has also been used to assess treatment results of individual cases. Outside of the typical occlusal traits considered in the previously mentioned classification systems, it implies the need to also consider lateral and panoramic cephalometric variables. What is unique in it is that it considers that different categories have a relatively different overall impact. In this sense, less points is better.

5.2.3 Malocclusion Classification in Epidemiological Settings

Mostly due to the absence of craniofacial imaging or the possibility to reassess or consider adjunctive diagnostic tools sometime after the initial clinical assessment, the epidemiological malocclusion classification systems/indices do focus on static occlusal conditions and more recently on the perceived impact of the malocclusion conditions on the assessed individuals.

We should first consider some of the requirements of an ideal index as per World Health Organization [14]:

1. Classification on a limited scale (with upper/lower limits).
2. Index equally sensitive throughout the scale.
3. A scale should represent closely clinical importance.
4. An index must be simple, quick, reproducible, and accurate.
5. Minimal judgment should be involved.

A series of earlier attempts were made to generate useful epidemiological indices. Due to space constraints, we will provide more details on those commonly used and only provide some necessary information from the older ones in ◘ Table 5.1.

5.2.3.1 Index of Orthodontic Treatment Priority (Need) (IOTN)

The first significantly used epidemiological orthodontic index could be considered the Index of Orthodontic Treatment Priority (Need) (IOTN) published in 1989 [15]. This index is a measurement of initial malocclusion complexity not intended to provide a direct assessment of treatment results. It considered five needs for treatment grades (none, little, moderate, great, and very great). The focus is on anterior occlusal disturbances that likely have an impact on aesthetics perception. In most instances, grades four and five justify access to state-funded orthodontic treatment. One of the concerns with the tool is its aesthetic component (AC-IOTN) that consists of ten anterior clinical occlusal photos that the assessed individual must use as a reference to identify where in the scale he/she feels fits as a degree of aesthetic impairment. The concern is for the individual to try to match its own occlusal features to one of the ten photos instead of giving the assessor an idea where he/she fits in a 10-point scale from really aesthetic to terribly unaesthetic.

5.2.3.2 Peer Assessment Rating (PAR)

Two years later, in 1991, the Peer Assessment Rating (PAR) index was proposed by Richmond et al. [16]. It provides a single summary score for all occlusal anomalies in any given malocclusion, and it is based on how far a case deviates from normal alignment and occlusion. It can be used as an assessment tool before and after orthodontic treatment. Components considered are occlusal relationships in six segments, amount of contact point displacement between anterior teeth, open bite and *overjet* measurements, and midline deviations. There is even

5

Table 5.1 Main indices and criteria used to identify malocclusion traits according to author, year, and dentition stage

Author	Year	Index	Type	Classification traits	Dentition
Angle [8]	1899	Angle's classification	Clinical	*Normocclusion:* normal sagittal relationship *Class I:* Discrepancies not related to sagittal relationship *Class II:* Lower molar posterior to the upper molar (mandibular retrognathism) *Class III:* Lower molar anterior to the upper molar (mandibular prognathism)	Permanent
Grainger [19]	1955	TPI (Treatment Priority Index)	Clinical–epidemiological	Aesthetic impact, reduced mastication performance, trauma that predisposes to caries and periodontal disease, phonetic problems, and occlusal stability	Permanent
Dracker [20]	1960	HLDI (Handicapping Labiolingual Deviation Index)	Epidemiological	Tooth displacements, crowding, *overjet, overbite*, anterior open bite, crossbite, ectopic eruption, supernumerary teeth, and hypodontia	Permanent
Bjork and Helm [21]	1964	–	Clinical–epidemiological	Tooth eruption problems, crowding, intra-arch tooth position, and spacing	Permanent
Foster and Hamilton [22]	1969	–	Clinical–epidemiological	Spacing, crowding, molar and canine relationship, *overjet*, anterior crossbite, *overbite*, anterior open bite, posterior crossbite	Deciduous
Summers [23]	1971	OI (Occlusal Index)	Epidemiological	Divisions I and II: normal or distal molar relationship without an associated syndrome, A: *overjet*, open bite, B: *overjet*, posterior crossbite, diastema and midline deviation, C: congenitally missing incisors, D: tooth displacement, E: posterior open bite Division III: mesial molar relationship associated to a syndrome, F: *overjet*, posterior crossbite, diastema and midline deficiency and syndrome, G: mixed-dentition analysis and tooth displacement	Deciduous mixed permanent
Bezroukov et al. [24]	1979	–	Epidemiological	Number of missing teeth, supernumerary, dysmorphic incisors, ectopic eruption, crowding/spacing	Permanent
WHO [25]	1987	–	Epidemiological	Small crowding/spacing anterior segment, mild rotations (1), *overjet* equal or larger than 9 mm, anterior crossbite, open bite, midline deviation of 4 mm or more or crowding/spacing greater than 4 mm (2)	Deciduous permanent
Brook and Shaw [15]	1989	IOTN	Epidemiological	*Overjet*, *overbite*, open bite, crossbite, crowding, impacted teeth, cleft/lip palate, sagittal occlusion, and hypodontia	Permanent
Richmond et al. [16]	1992	PAR	Clinical–epidemiological	Contact displacement among anterior teeth, *overjet*, *overbite*, and midline deviation	Mixed permanent
Jenny et al./ WHO [17]	1997	DAI	Epidemiological	Missing anterior teeth, crowding/spacing in anterior segment, diastema, tooth displacements in anterior segment, *overjet*, open bite, and sagittal occlusion	Permanent
Daniels and Richmond [18]	2000	ICON	Clinical–epidemiological	Crowding/spacing, crossbite, sagittal occlusion, *overjet*, and *overbite*	Permanent

a modification for mixed-dentition cases. The most used subcomponent is the amount of anterior contact displacement which is sometimes inadvertently assumed as the whole purpose of the PAR index.

5.2.3.3 Dental Aesthetic Index (DAI)

The Dental Aesthetic Index (DAI) was suggested in 1996 by Jenny and Cons [17]. It is an epidemiological survey to identify unmet orthodontic treatment need. It considers the number of missing visible teeth, the amount of crowding/spacing in the anterior occlusal segments, midline diastemas, sagittal posterior occlusion, overjet, and overbite. A weighted score is assigned to each of these categories plus a constant number (13 points). A score of 26 is used to separate handicapping malocclusions. It was proposed that this index is a link between the public's perception of dental aesthetics and objective measurements associated with malocclusion.

5.2.3.4 Index of Complexity, Outcome, and Need (ICON)

The Index of Complexity Outcome and Need (ICON) was proposed in 2000 [18]. It was the first epidemiological orthodontic index to clearly consider outcome as a key component. In other words, it can simultaneously measure malocclusion complexity, need, and treatment outcome. It uses the same aesthetic scale as the AC of the IOTN (with the same associated concerns) and focuses on upper/lower arch crowding/spacing, crossbite, open bite, *overjet*, and posterior sagittal occlusion. Scoring up to 5 points is assigned for each of these categories to come with a final overall score.

5.2.4 Summary

In summary, although historically malocclusion classifications have evolved from a simple analysis of the occlusal relationship between opposing teeth to progressive consideration of skeletal and soft-tissue components in a 3D analysis, the reality is that all these systems still rely on a static analysis of the multiple parts without proper consideration about how these parts do function together. Temporomandibular joint (TMJ) assessment, teeth contacts during disocclusion movements, and oral functions (breathing, speech, and swallowing) among others are all factors that certainly should influence a comprehensive occlusal assessment of any individual. These are not considered part of almost any of the abovementioned indices.

Although malocclusion classifications were developed specifically for individual assessment of patients requesting orthodontic treatment, sometimes they have been used for epidemiological assessments and vice versa. This generates problems with the validity of the data collected by using an inappropriate not specifically validated tool for a given task.

Some interesting philosophical questions that remind partially unsolved are the fact that it is more frequent to have a malocclusion than not have one, how critical is it to have a Class I molar occlusion, is a 1–2 mm difference in any direction a major occlusal problem? Nevertheless, those seem to be consistently considered cornerstone pieces of the occlusal assessment in both the clinical and epidemiological assessments of malocclusion.

5.3 Epidemiology

5.3.1 Deciduous Dentition

Estimates of different occlusal features in the deciduous dentition can be observed through numerous studies, mainly from northern Europe, the United States, and more recently from some countries of South America and Asia, such as Brazil and China.

One of the earliest studies focusing on deciduous dentition was conducted in Rome, Italy, around 1912. By studying the occlusion of 1000 children aged 3–6 years, Chiavaro [26] found 28.9% of malocclusion cases in which 14.2% were Class II deviations and 9.0% were Class III. He concluded that the most common irregularities in the permanent dentition could also be found in the temporary dentition.

Throughout the twentieth century, stronger epidemiological concepts were applied, and among related aspects, there was an increase in both the size of the study populations and their range and representativeness.

One of the first studies involving an extensive sample of children in the deciduous dentition period was published in 1950. The authors examined 3380 British children of whom approximately 500 were between 2 and 2.5 years of age. They observed that in this specific group, 41.4% of children had an irreproducible mandibular position [27].

Although from a small sample, a study conducted in Birmingham, England, deserves to be highlighted by its influence in establishing criteria for measuring occlusal problems in the deciduous dentition used in subsequent

research. Foster and Hamilton [22] visited ten public child health clinics. One hundred white children were examined in the age group from two and a half to three years. Findings showed 72% of cases with increased incisor overjet and 45.0% having Class II primary canine relationship.

A PubMed searching (October 17, 2018) for "Malocclusion" AND "Prevalence" AND "Dentition, Deciduous" revealed 159 studies, most of them (n = 107) were from the year 2000 onward.

Despite many studies, there are only a few studies from those 107 that present a population-based research design. Moreover, a direct comparison among the results found in the surveys is difficult due to the variation in the adopted criteria, in the classification categories of malocclusion severity, and differences among the samples regarding age, sex, and ethnicity.

In this sense, part of the variation observed during the early stages of occlusion development may not be attributed solely to the interaction between genetic and environmental factors acting during orofacial growth and development, but also to differences in the interpretation criteria of what represents occlusal deviation that may adversely affect the permanent dentition resulting in a malocclusion.

To overcome the difficulty of comparing the studies, some experts stressed the need for the scientific community to reach a consensus about interpretation criteria of what constitutes a problem of dental occlusion from a public health perspective [28].

Caution should be exercised when only indices based on purely clinical criteria are adopted. These indices do not consider the degree of treatment need as related to the inclusion of an individual in society and, consequently, they are not satisfactory for use in public health–related research.

Table 5.2 describes results from several population-based studies from the year 2000 onward. Interestingly, the prevalence of any type malocclusion varied from 50.0% to 83.9%: anterior open bite varied from 1.0% to 50.0% and posterior crossbite varied from 0.4% to 20.8%.

Table 5.2 Population-based study of malocclusion prevalence and sample characteristics in deciduous dentition from 2000

Authors	Year[a]	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
Thilander et al. [30]	2001	Bogotá, Colombia	373	[b]	Any type	49.4	10.7	7.2
					Molar relation (Classes II; III)	15.5; 2.9		
					Overjet >4 mm	18.0		
Katz et al. [31]	2004	Recife, Brazil	330	4	Any type	49.7		
					Overjet	29.7	36.4	12.1
Peres et al. [32, 33]	2007	Pelotas, Brazil	359	5 a 6			46.3 [32]	18.2 [33]
Batwala et al. [34]	2007	Mbarara, Uganda	142	5 a 6	Overjet >8.9 mm	14.8		
Grabowski et al. [35]	2007	Rostock, Germany	766	4.5(0.9)[c]	Any type	74.7	11.4	7.2
					Classes II; III molar	25.8; 1.3		
					Overjet >2 mm	49.3		
					Overbite >2 mm	33.2		
Silva Filho et al. [36]	2007	Bauru, Brazil	2016	3 a 6	Any type	73.3		20.8
Almeida et al. [28]	2008	Mauá, Brazil	344	3 a 5	Molar relation (distal; mesial step)	9.7; 6.0	27.9	11.3
					Canine relation (Classes II; III)	11.0; 2.9		
					Overjet >3.0 mm	16.0		
					Overbite >3.0 mm	7.0		

Table 5.2 (continued)

Authors	Year[a]	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
Hebling et al. [37]	2008	Piracicaba, Brazil	728	5			32.4	17.1
Macena et al. [38]	2009	Recife, Brazil	2750	18–59[a]				10.4
Dimberg et al. [6]	2010	Orebro, Sweden	457	3	Any type	70.0	50.0	19.0
					Classes II; III molar	26.0; 9.0		
					Overjet (>4 mm)	23.0		
Berneburg et al. [39]	2010	Baden-Württemberg,	2016	4 a 6	Canine relation (Classes II; III)	22.7; 4.8	4.6	10.7
		Germany			Overjet >2.5 mm	16.5		
					Overbite	25.5		
Bhayya, Shyagali [40]	2011	Bagalkot City, India	1000	4–6	Molar relation (distal; mesial step)	8.4; 35.9	1.0	0.6
					Canine relation (Classes II; III)	14.2; 0.3		
					Overjet >2.0 mm	15.5		
					Overbite >2.0 mm	18.4		
Carvalho et al. [41]	2011	Belo Horizonte,	1069	5	Any type	46.2	7.9	13.1
		Brazil			Overjet >2 mm	10.5		
					Overbite >2 mm	19.7		
Romero et al. [42]	2011	São Paulo, Brazil	1377	3–6	Open bite	22.4		
Marquezan et al. [43]	2011	Canoas, Brazil	890	3–6	Overjet >2 mm	61.5	38.3	15.2
Vasconcelos et al. [44]	2011	Recife, Brazil	1308	30–59[d]	Open bite	30.4		
Seemann et al. [45]	2011	Rostock, Deutschland	766	4.0(1.0)[c]	Crowding	10.8	14.3	
Urzal et al. [46]	2013	Porto (Paranhos), Portugal	189	3–6	Bilateral mesial step	40.3	16.9	0.4
Baral et al. [47]	2014	Kaski District, Nepal	506	3–5	Bilateral distal steps	8.5		
					Mesial step one side	12.7		
					Mesial step one side and distal step other	2.6		
					Distal step one side	2.4		
					Anterior crossbite	3.0		
					Any type	62.4	21.0	11.6
Sousa et al. [48]	2014	Campina Grande	732	3–5	Increased overjet	42.6		

(continued)

Table 5.2 (continued)

Authors	Year[a]	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
		Brazil			Anterior open bite	21.0		
					Deep overbite	19.3		
					Any type	81.4		
Normando et al. [49]	2015	Belém, Brazil	652	3–6	Molar relation (distal; mesial step)	4.0; 31.0		
Souza et al. [50]	2015	Amazon indigenous populations						
		Assurini village	28		Malocclusion	37.7	3.6	3.2
					Class II; Class III	7.1; 3.6		
					Overjet >3 mm	7.1		
		Pat-krô village	15		Malocclusion	46.7	0.0	0.0
					Class II; Class III	33.3; 0.0		
					Overjet >3 mm	33.3		
		Pikayaka village	10		Malocclusion	10.0	0.0	0.0
					Class II; Class III	10.0; 0.0		
					Overjet >3 mm	10.0		
Shavi et al. [51]	2015	Davangere, India	945	6	Distoclusion	36.5	6.9	7.6
Zhou et al. [52]	2016	Xi'an, China	2974	2.6–6.1	Any type	83.9		
					Deep overbite	37.6		
					Midline deviation	25.3		
					Anterior crossbite	6.8		
Zhou et al. [52]	2017	Shanghai, China	2335	3–5	Deep overbite	63.7		
					Deep overjet	33.9		
					Midline deviation	26.6		
					Anterior crossbite	8.0		
					Anterior crowding	6.5		

[a]Year of publication
[b]Age not informed, but development stage related to deciduous dentition
[c]Mean (standard deviation)
[d]Months

Shen et al. [29] published a meta-analysis synthesizing the magnitude of malocclusion among children aged 2–7 years in mainland China from 1988 to 2017. Based on 31 studies describing 51,100 participants, the pooled malocclusion prevalence was 45.5% (95% confidence interval (CI): 38.1–52.8%) with 26.5% Class I (CI: 19.9–33.1%), 7.9% Class II (CI: 6.1–9.9%), and 12.6% Class III (CI: 9.5–15.7%) cases. The most common type of malocclusion trait was increased overbite (33.7%, CI: 27.7–39.7%), and a flush terminal plane type (47.1%, CI: 28.8–65.4%) was the most common in the terminal plane relationship. Other deviations were deep overbite 33.66% (CI: 27.66–39.67%),

anterior crossbite 25.29% (CI: 20.01–30.58%), deep overjet 10.16% (CI: 4.19–16.12%), anterior open bite 3.36% (CI: 2.24–4.48%), and posterior crossbite 2.81% (CI: 1.8–4.53%). An increasing trend in deciduous-dentition malocclusion over time and a wide variation of this condition across the country was observed.

5.3.2 Mixed Dentition

Due to extreme biological dynamism, prevalence estimates of malocclusion during mixed dentition are quite diverse. Individual variations during dental development at this stage may make it difficult to distinguish between normal variations from malocclusion traits with low self-correcting potential from those that oscillate with age, as in the case of anterior open bite, natural bite closure is observed from 3 to 7 years of age. Therefore, prevalence data can present significant challenges both for observation and for interpretation when faced with a series of occlusal traits that may be temporarily altered but that eventually may improve.

One of the first population-based studies including children with mixed dentition was published in 1956. Of the 3355 American children examined from 6 to 14 years of age, half (52%) had some degree of occlusal deviation and one in each five was among the most severe types whose malocclusion could hardly be avoided or self-corrected and likely will need corrective orthodontics [53].

A PubMed searching (October 17, 2018) for "Malocclusion" AND "Prevalence" AND "Dentition, Mixed" provided 59 items, most of them (n = 42) were from the year 2000 onward. Despite the difficulties noted in measuring malocclusion during mixed dentition, the interest in population-based studies has never been so great as in the two first decades of the twenty-first century. Table 5.3 summarizes results from several mixed-dentition population-based studies. The prevalence of any type malocclusion varied from 34.7% to 92.7%: anterior open bite ranged from 4.5% to 50.0% and posterior crossbite from 4.8% to 23.3%. It must be noted that results from a study in a sample of 10-year-old New Zealand children led the authors to raise some questions about the suitability of the DAI as a tool to

Table 5.3 Population-based study of malocclusion prevalence and sample characteristics in mixed dentition

Authors	Publication year	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
Johnson and Harkness [54]	2000	New Zealand	294	10	Mandatory treatment need	33.3		
Thilander et al. [30]	2001	Bogotá, Colombia	1539	[a]	Any type	57.7	11.4	4.0
					Molar relation (Classes II; III)	20.4; 3.9		
					Overjet >4 mm	17.4		
			1371	[b]	Any type	78.0	6.2	3.7
					Molar relation (Classes II; III)	24.9; 3.5		
					Overjet >4 mm	29.7		
Keski-Nisula et al. [55]	2003	3 rural municipalities,	489	4–7.8	Any type	92.7	39.1	7.5
		Finland			Mesial and distal step	19.1; 33.1		
					Canine relation (Classes II; III)	52.4; 1.5		
					Overjet (>= 4 mm)	26.7		
					Overbite	33.8		
					Overjet and overbite (>= 4 mm)	15.5		

(continued)

Table 5.3 (continued)

Authors	Publication year	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
Tausche et al. [56]	2004	Dresden, Germany	1975	6–8	Great treatment need	26.2	17.7	8.2
					Deep overbite	46.2		
					Overjet	37.5		
					Reversed overjet	3.2		
Glasl et al. [57]	2006	Frankfurt am Main,	1251	9–11	Any treatment need	41.4	4.7	15.3
		Germany			Overjet negative	14.9		
					Overjet >6 mm	17.4		
Grabowski et al. [35]	2007	Rostock, Alemanha	2275	8.3 (1.4)[c]	Any type	92.7	9.5	12.0
					Classes II; III molar	31.4; 3.9		
					Overjet >2 mm	59.0		
					Overbite >2 mm	46.8		
Perinetti et al. [58]	2008	Region of Abruzzo,	1198	7–11	Any type	90.0	18.7[d]	14.3
		Italy			Classes II; III molar	16.8; 6.3		
					Increased overjet	45.0		
Grando et al. [59]	2008	Goiás, Brazil	926	8–12	Molar relation (Classes II; III)	21.7; 11.3	6.6	4.3
Dias and Gleiser [60]	2009	Nova Friburgo, RJ	407	9–12	Treatment need		14.5	33.7
					Moderate/definite	23.1		
					Increased overjet	29.7		
					Reverse overjet	3.9		
Martins and Lima [61]	2009	Fortaleza, Ceará	264	10–12	Molar relation (Classes II; III)	22.3; 4.2	36.7	
					Overjet	50.0		
Seemann et al. [45]	2011	Rostock, Deutschland	2209	7.8(1.4) [c]	Crowding	49.7		
Dimberg et al. [62]	2013	Orebro, Suécia	386	7	Any type	58.0	10.0	14.0
					Classes II; III – molar	28.0; 5.0		
					Overjet (>4 mm)	17.0		
Grippaudo et al. [63]	2013	Rome, Italy	3017	7–13	3, 4, and 5 grades	75.8		
Urzal et al. [46]	2013	Porto (Paranhos), Portugal	379	7–12			11.3	
Shalish et al. [64]	2013	Jerusalem, Israel	432	7–11	Any treatment need	34.7	6.5	23.3

Table 5.3 (continued)

Authors	Publication year	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
					Anterior crossbite	9.5		
					Molar relation (Class III)	3.0		
					Overjet (=7 mm)	3.7		
					Impinging overbite	5.2		
					Crowding >5 mm (Max; Mand.)	6.9; 6.0		
Souza et al. [50]	2015	Amazon indigenous populations						
		Assurini village	21		Malocclusion	66.7	9.5	4.8
					Class II; Class III	9.5; 4.8		
					Overjet >3 mm	4.8		
		Pat-krô village	20		Malocclusion	60.0	5.0	5.0
					Class II; Class III	35.0; 0.0		
					Overjet >3 mm	30.0		
		Pikayaka village	6		Malocclusion	66.7	50.0	16.7
					Class II; Class III	16.7; 0.0		
					Overjet >3 mm	0.0		

[a]Age not informed, but development stage related to early mixed dentition
[b]Age not informed, but the development stage related to late mixed dentition
[c]Mean (standard deviation)
[d]Included those having less than the incisal third of the mandibular central incisor crown overlapped by maxillary central incisor crown, including an edge-to-edge or open bite relationship

assess orthodontic treatment need in mixed-dentition samples [54]. This implies that some of the available diagnostic methods may not be ideally suitable for proper prevalence determination in this specific age range.

The depicted estimates show high variation and values that indicate that the prevalence may be high, suggesting a careful approach when deciding early intervention. As the genesis of most of these deviations is related to orofacial development stages that occur during deciduous dentition, the introduction of specific preventive activities in maternal–childhood programs directed to oral-facial development from ages 0–6 are measures that should be considered in the normative and strategic planning carried out in health-care systems. "Early treatment of caries and preventive programs including oral hygiene, use of fluoride, and control of environmental factors associated to malocclusion such as short-term breastfeeding, premature tooth loss, respiratory infection, deleterious suction habits, dietary lower consistency, seem still to be the best means of reducing the high prevalence of malocclusion. Methods of intervention should be investigated and implemented as early as possible to increase the proportion of normal occlusion population on the one hand, and on the other hand, to reduce the proportion of moderate/severe malocclusion to levels which are socially more acceptable and economically sustainable. Treatments of more severe cases are recommended not only in the permanent dentition but also in the deciduous/mixed dentition" [1]. It is waiting until the mixed dentition would not maximize the preventive potential of some of these measurements.

5.3.3 Permanent Dentition

The investigations on malocclusion distribution during permanent dentition among different populations reveal substantial differences in prevalence rates. Despite this, there is evidence of an increase in both malocclusion prevalence and severity, from medieval times up to date. Identified studies suggest that poor tooth positioning has increased in the last 150 years, especially in civilizations that have experienced rapid technological advancement and in rural populations whose natural diet has been replaced by a softer, cheer-free diet, typical of urban populations [65]. These changes, also known as secular trends, are also observed associated with other phenomena in the Western world as, for instance, weight, height, and onset of puberty [66]. Investigating occlusal patterns in two generations of children, Brin et al. [67] found a decrease in the prevalence of normal occlusion accompanied by an increase of Class I malocclusion. No difference was noted concerning molar and canine anteroposterior relationships.

A PubMed search (January 16, 2019) for "Malocclusion" [MeSH Terms] AND "Prevalence" [MeSH Terms] AND "adolescent" [MeSH Terms] provided 334 items, most of them (n = 235) were from year the 2000 onward. From them, we identified 30 population-based studies related to permanent dentition. Based on their supporting references, ten studies were manually added (Table 5.4). When two studies of the same city were found, only the most recent one was included. Data from subpopulations related to a specific sex or ethnicity within a larger population or from an age group that included the mixed dentition without the possibility of obtaining stratified information were not considered.

Table 5.4 shows the main features of population-based epidemiologic studies in which high variation among prevalence estimates can be identified. Prevalence of any type of malocclusion varied from 19.0% at Kadiogo, Burkina Faso [68], to 93.0% at Foggia, Italy [69]. The variation range of absolute values seems to be reduced for certain malocclusion traits and more specific occlusal deviations. Based on grades four and five of IOTN, the prevalence varied from 28.7% at Kirikkale, Turkey [70], to 43.8% at Tirana, Albania [71]. Anterior open bite varied from 1.0% in Kuwait [72] to 15.0% at Tanzania [73]. The prevalence rates of severe/very severe malocclusion measured by Dental Aesthetic Index varied from 4.0% at Shimla city, India [74], to 41.3% at Lagos, Nigeria [75].

5.4 Protective Factors and Risk Indicators for Malocclusions

Malocclusions have often resulted from a complex interaction among several factors, which influence the growth and development of the craniofacial bones and teeth. Contemporary research reinforces the importance of a balanced view of genetic, environmental, and behavioral aspects when understanding the development of malocclusions [3].

Concerning genetic issues, the efficacy of preventive interventions is questionable. Alternatively, for the behavioral factors that influence the development of dental arches and the adequate positioning of teeth during childhood effective prevention, measures may contribute to the establishment of a satisfactory occlusion. Moreover, this section focuses on the environmental characteristics associated with malocclusion.

5.4.1 Socioeconomic Conditions

The influence of socioeconomic conditions on the development of malocclusion is controversial, and the literature about this topic can still be considered scarce.

Regarding overall malocclusion classification, a few studies investigated the impact of socioeconomic status (SES). A study conducted in the United States with white children aged 2.5–6 years found that the prevalence of Angle's Class II malocclusion in girls with low socioeconomic status was higher (18.4%) than that found in girls with an intermediate socioeconomic status (15.3%). Also, a higher prevalence of posterior crossbite was observed among children belonging to the intermediate social stratum when compared to children from lower social level [104]. Brazilian adolescents who self-reported having black/brown skin color and those from low household income were more likely to present severe malocclusion than their counterparts [99]. Similar findings were found in other regions of Brazil such as Minas Gerais [102] where the type of school was used as a proxy for socioeconomic status (SES), showing those from private schools with less chance to present severe malocclusion.

The presence of harmful oral habits, admittedly associated with occlusal problems, seems to be associated with more general determinants. Deleterious oral habits are inversely associated with socioeconomic conditions represented by categories related to income, schooling, maternal work, and occupation [37].

Finally, longitudinal studies have failed to identify the significant impact of SES. A birth cohort study including 3-year-old Thuringian children in Germany identified no association between migration background

Table 5.4 Population-based study of malocclusion prevalence and sample characteristics in permanent dentition

Authors	Year[a]	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
Szöke and Petersen [76]	2000	8 districts, Hungary	900	12	Moderate/severe	23.1		
Tapsoba, Bakayoko-Ly [68]	2000	Kadiogo, Burkina Faso	300	12	Any type	19.0		
Goel et al. [77]	2000	Puttur, Índia	200	12–13	Any type	36.9		
Thilander et al. [30]	2001	Bogotá, Colombia	1441	[b]	Any type	71.5	8.7	3.9
					Molar relation (Classes II; III)	18.5; 4.9	4.9	
					Overjet >4 mm	25.9		
Esa et al. [78]	2001	Klang District, Malaysia	1512	12–13	Severe/very severe	17.8	2.0	
					Overjet >4 mm	41.5		
Onyeaso [79]	2004	Ibadan, Niger	636	12–17	Molar relation (Classes II; III)	14.0; 12.0		
Baca-Garcia et al. [80]	2004	Granada, Spain	744	14–20	Severe/very severe	21.1		
					Overjet >4 mm	19.8	3.6	
Alkhatib et al. [81]	2005	Two boroughs, North West London, England	2346	12–14	Treatment need	32.0		
Behbehani et al. [82]	2005	Kuwait	1299	13–14	Moderate/severe	71.0	3.4	25.2
					Molar relation (Classes II; III)	31.2; 11.0		
					Overjet >3.5 mm	42.8		
Van Wyk and Drumond [83]	2005	7 Provinces, South Africa	6142	12	Severe/very severe	31.0		
Ciuffolo et al. [69]	2005	Foggia, Italy	810	11–14	Any type	93.0	1.7	12.2
					Overjet >3 mm	19.1		
Abu Alhaija et al. [84]	2005	Irbid, Jordan	1003	13–15	Any type	92.0	2.9	7.1
					Molar relation (Classes II; III)	17.5; 1.4		
					Overjet >3 mm	24.7		
Gábris et al. [85]	2006	Budapest and Debrecen	483	16–18	Any type	70.4	10.8	11.6
		Hungary			Molar relation (Classes II; III)	39.1; 8.1		
Frazão and Narvai [86]	2006	São Paulo state, Brazil	8837	12	Severe/very severe	18.0		
			4964	18	Severe/very severe	13.7		
Rwakatema et al. [87]	2006	Moshi, Tanzania	289	12–15	Severe/very severe	13.8	6.2	

(continued)

Table 5.4 (continued)

Authors	Year[a]	Place	Sample	Age	Malocclusion Category	Prevalence (%)	Open bite	Posterior crossbite
					Maxillary median diastema	20.1		
Dhar et al. [88]	2007	Udaipur, India	812	11–14	Severe	7.9		
Manzanera et al. [89]	2009	Valencian, Spain	363	12	Definite treatment need	23.5		
			292	15–16	Definite treatment need	18.5		
Shivakumar et al. [90]	2009	Davangere, India	1000	12–15	Severe/very severe	4.2	2.1	
					Overjet	6.9		
Mtaya et al. [73]	2009	Kinondoni and Temeke	1601	12–14	Any type	63.8	15.0	5.1
		Districts, Tanzania			Molar relation (Classes II; III)	4.4; 2.0		
					Overjet >4 mm	11.5		
Borzabadi-Farahani et al. [91]	2009	Isfahan, Iran	502	11–14	Any type	77.1	1.6	10.4
					Molar relation (Classes II; III)	24.1; 7.8		
					Overjet ≥3.5 mm	28.1		
					Overbite	34.5		
Eslamipour et al. [92]	2010	Isfahan, Iran	728	11–20	Severe/very severe	21.9		
Al-Azemi et al. [72]	2010	Kuwait	1481	13–14	Treatment need	31.1	1.0	3.0
					Overjet >3.5 mm	8.6		
Nagarajan et al. [93]	2010	Bangalore, India	1618	14–15	Severe/very severe	6.9		
Anosike et al. [75]	2010	Lagos, Nigeria	805	12–16	Severe/very severe	41.3	7.0	
					Overjet >3 mm	32.5		
Murshid et al. [94]	2010	Jeddah, Saudi Arabian	1024	13–14	Any type	81.0		
					Molar relation (Classes II; III)	21.0; 15.0		
					Overjet (4–6 mm; >6 mm)	24.0; 5.0		
					Overbite (4–6 mm; >6 mm)	27.0; 13.0		
Peres et al. [95]	2010	Pelotas, Brazil	339	12	Treatment need	40.2	7.4	
Singh et al. [96]	2011	Udupi district, South India	927	12	Severe/very severe	5.0	1.8	
					Overjet >2 mm	11.7		

Bhardwaj et al. [74]	2011	Shimla city, India	622	16–17	Severe/very severe	4.0	1.0	
					Overjet >2 mm	27.1		
Phaphe et al. [97]	2012	Bagalkot city, India	1000	12–14	Any type	50.0		
					Molar relation (Classes II; III)	30.1; 1.6		
					Overjet >4 mm	15.2		
Muasya et al. [98]	2012	Nairobi, Kenya	1382	12–15	Severe/very severe	24.0	14.0	
					Overjet >3 mm	36.4		
					Anterior crossbite	6.2		
Laganà et al. [71]	2013	Tirana, Albania	1260	12–15	Treatment need	43.8		
					Molar relation (Classes II; III)	31.8; 2.9		
Peres et al. [99]	2013	Brazil	7328	12	Very severe	6.5		
			5445	15–19	Very severe	9.1		
Aikins et al. [100]	2014	Rivers State, Nigeria	620	13–20	Any type	88.2	7.1	17.1[c]
					Molar relation (Classes II; III)	6.3; 1.6		
					Overjet >4 mm	15.6		
Spalj et al. [101]	2014	Zagreb, Croatia	691	12	Severe/very severe	14.6	2.5	13.0
					Overjet >3 mm	30.9		
			351	18	Severe/very severe	10.8	3.7	14.5
					Overjet >3 mm	16.8		
Bilgic et al. [70]	2015	Kirikkale, Turkey	2329	12–16	Treatment need	28.7	8.2	9.5
					Molar relation (Classes II; III)	44.7; 10.3		
					Overjet	25.1		
Silveira et al. [102]	2016	Montes Claros, Brazil	763	15–19	Severe/very severe	12.6	4.2	
					Overjet >3 mm	19.6		
Goettems et al. [103]	2018	Uruguay	278	15–24	Severe/very severe	15.8		

[a]Year of publication
[b]Age not informed, but development stage related to permanent dentition
[c]Anterior and posterior crossbite

as a SES proxy with malocclusion traits such as open bite, increased overjet, overbite, and crossbite [105], corroborating findings from birth cohort studies in Brazil [32, 33].

No association between parental education and the need for orthodontic treatment was found among 10–12-year-old children in a suburb of Boston, USA [106], and among schoolchildren aged 5–7 years in Delhi, India [107], when conditions such as family size, parental occupation, location, and type of school were studied.

In summary, few papers have suggested that there is no association between different SES proxies and malocclusion in general terms. Nevertheless, when specific occlusal traits are considered, some associations are found originated from cross-sectional studies. This could be explained as the fact that when malocclusion is classified as an overall measure, the impact of individual traits is diluted. However, findings from longitudinal studies do not support such an assumption.

5.4.2 Anthropometric Characteristics

Anthropometric measurements in children, such as birth weight, head circumference, weight/height ratio, among others, have been considered as factors that influence the development of individuals, predisposing them to diseases in childhood and adult life such as dental caries [108].

Regarding malocclusion, there is little evidence on the contribution of anthropometric measures to the development of occlusal problems. However, it is recognized that these factors may be associated with deficits in skeletal growth, which would predispose to poor dental positioning. Moreover, insufficient bone development may interfere in the maturity of the oral musculature during the first years of life. A study developed in São Luis (Brazil) identified an association between nutritional deficit and dental crowding in the deciduous dentition in children aged 3–5 years. Children without a pacifier habit and with a deficiency in the relation weight by height and height by age presented a greater chance of dental crowding than those free of these deficient nutritional characteristics [109].

Preterm birth is often related to exposure to oral intubation, which may lead to structural alterations of skeletal development causing defects in both primary and permanent dentition. High-arched palate and palatal asymmetry have been positively associated with preterm children [110]. A more recent and well-designed study carried out in France found preterm birth positively associated with the presence of crossbite at 3 years of age [111]. However, no association between preterm and malocclusion was found when children at the same age were investigated in Germany [105].

Changes in head circumference and gestational age seem directly contribute to the development of malocclusion. A cross-sectional study nested in a cohort study including 350 children in a specific region of Northeast Brazil revealed that factors related to growth as height/age ratio and head circumference in the first 6 years of life were associated with the development of malocclusion. Children who have gained less than one standard deviation concerning the mean gain in head circumference and those who had less than 1 Z – score gain for height/age ratio were, respectively, 16% and nearly three times more likely to have malocclusion at six years of age than their counterparts [112].

Several studies have investigated the potential effect of inadequate nutrition and dental development. The mechanism by which malnutrition could impact malocclusion may be linked to at least two pathways. One may be by increase in caries predisposition, which may lead to loss of interproximal contact points. A second pathway between malnutrition and malocclusions would be through the delay in tooth eruption [113]. Early in the 1990s, research using data from a longitudinal study in Peru suggested that malnourished children had an increased risk of caries and delay in tooth eruption [113]. Pairs of emerged teeth at 12 months and the emergence stage of first permanent molars at 6 years of age were also associated with stunting at 6 months of age [114]. Early childhood protein-energy malnutrition conditions a delayed emergence of deciduous and permanent teeth later in life. This was confirmed in India in cross-sectional studies where most subgroups of stunted boys and girls had fewer emerged deciduous teeth than their counterparts. Authors concluded that even moderate malnutrition could delay deciduous tooth emergence. The same group assessed an older sample from the same area, identifying earlier during the emergence of the first set of permanent teeth that stunted children had delayed emergence. This difference disappeared at later stages of dental development [115].

5.4.3 Child Behavior

Among several behavioral factors that may lead to the development of malocclusions, oral habits are the most supported by scientific evidence, especially non-nutritive sucking habits, which vary according to the population's cultural characteristics. In Western countries, the practice of sucking a pacifier is prevalent in up to 95% of children. However, in parts of Asia and Africa and more specific population groups, such as Eskimos, this may be rare or even unknown [116]. The persistence of this habit

has been associated with different degrees of deformities in the orofacial structures and, consequently, in the occlusion of the deciduous and permanent dentition.

Pacifier use and finger and thumb suction have stood out among the most documented habits. Among the types of occlusal deviations related to these habits that have been reported are anterior open bite, anterior and posterior crossbite, increased overjet, and disto-occlusion.

A systematic review aimed to analyze the effects of pacifier sucking on orofacial structures, including the evidence of differences between orthodontic and conventional pacifiers found moderate evidence on the association between the presence of anterior open bite and the use of a pacifier when compared with their counterparts. The duration and frequency of pacifier use played an essential role in the development of this type of malocclusion. Also, the authors highlighted that pacifiers with thin neck induce less open bite than the conventional ones [117]. Another recent systematic review [118] discussed the potential prevention potential of using an orthodontic pacifier instead of a conventional one at earlier ages. Their conclusion is that there is no substantial evidence that one works better than the other.

When only longitudinal studies which investigated the anterior open bite is considered, a significant variation relative to age groups, the frequency of use of a pacifier, and the type of pacifier evaluated are found. Many of these studies identified a strong association between the presence of anterior open bite and the use a pacifier when compared with children not using a pacifier [105, 119–121]. The risk of anterior open bite remained even after the discontinued use of a pacifier at 1 year of age [121]. Moreover, longer duration of pacifier sucking was associated with anterior open bite [32] against no sucking or shorter period of sucking. A recent systematic review [122] discussed the potential of self-correction of the anterior open bite when the deleterious habit is controlled. The use of crib appliance seems to be the better-supported approach [122].

Findings from longitudinal studies on the association between the use of a pacifier and posterior crossbite are controversial. Prolonged pacifier habits resulted in changes to the dental arches and the occlusal parameters, and these changes persisted well beyond the cessation of the pacifier in children aged 4–5 years [123]. This finding is supported by other studies, which also found a higher prevalence of crossbite among Brazilian children who used a pacifier up to 6 years of age [33] and in 3-year-old children from Bristol, UK [120]. On the other hand, difference concerning posterior crossbite between the subjects who used pacifier and those who did not use a pacifier at 12, 18, and 30 months was not significantly different in 2.5-year-old children [121].

Most studies which investigated the association between other malocclusions, such as overjet, and disto-occlusion and the use of a pacifier are cross-sectional studies. One exception is the study from Moimaz et al. [121], which found a higher prevalence of overjet in children aged 2.5 years associated with a pacifier-sucking habit at 12, 18, and 30 months after birth. Moreover, another longitudinal study found pacifier habits causing significant changes to dental arch parameters such as increased mandibular arch width and a decrease in maxillary arch width in children aged 4–5 years.

Digit sucking and thumb sucking are common non-nutritive sucking habits that increase the risk to the development of Class II canine relationship, overjet, posterior crossbite, and open bite. The use of a pacifier is nearly three times less harmful for the occurrence of overjet than digit-sucking habit. However, children using a pacifier are four times more likely to present Class II canine relationship and posterior crossbite than those with digit or thumb sucking [124].

Table 5.5 shows longitudinal studies or cross-sectional studies nested in cohort studies on the association between any non-nutritive sucking habits and malocclusion published from 2008 onward.

5.4.4 Maternal Characteristics

The 2016 Lancet series on breastfeeding emphasizes that breast milk makes the world healthier, smarter, and more equal. For mothers, breastfeeding has been associated with protection against obesity, diabetes, and cancer. For children, any breastfeeding may prevent diarrhea and pneumonia as well as increase the child IQ of 2.6 points [126]. Oral health can also benefit from breastfeeding, and malocclusion is one of the long-term health outcomes potentially associated with breast milk. Studies have shown that breastfeeding promotes the appropriate development of the jaws and strengthens the muscles involved in the suckling process of breast milk. Suckling movements that occur during breastfeeding involve tongue peristaltic motions around the breast nipples that can help guide palate morphology by rounding and flattening it [127]. Moreover, the shape of the halo of the maternal breast adapts to the internal format of the child's mouth, allowing a perfect oral sealing [128].

A systematic review of the association between malocclusion in deciduous dentition and breastfeeding compared different exposures to breastfeeding as a potential protective factor to malocclusion. The authors concluded that breastfeeding compared with the absence of breastfeeding decreased the odds of developing a nonspecific malocclusion by 66%, that exclusive breastfeeding versus nonexclusive breastfeeding decreased the odds of developing a nonspecific malocclusion by 46%, and that a more extended breastfeeding period decreased the odds of developing a nonspecific malocclusion by 60% [129].

Table 5.5 Nonsucking habits (NSH) associated with malocclusion from cohort studies, 2008–2018

Author (s)	Country	Year	*n*	Age (outcome)	NSH	Type of malocclusion
Duncan et al. [120]	United Kingdom	2008	867	15–36 m	Pacifier	Anterior open bite Posterior crossbite
Heimer et al. [119]	Recife, Brazil	2008	287	4–6 yr	Digit sucking Pacifier	Anterior open bite Posterior crossbite
Onyeaso and Isiekwe [79]	Nigeria	2008	145	3–5 yr	Digit sucking	Anterior open bite
Dimberg et al. [125]	Sweden	2010	386	3–7 yr	Digit sucking Thumb sucking or others	Anterior open bite Posterior crossbite
Moimaz et al. [121]	Sao Paulo, Brazil	2014	80	30 m	Pacifier Finger sucking	Overjet Anterior crossbite Overbite Open bite Posterior crossbite
Peres et al. [33]	Brazil, Pelotas	2015	1124	5 yr	Pacifier	Open bite Crossbite Overjet Moderate/severe malocclusion (WHO criteria)
Wagner and Heinrich-Weltzien[a] [105]	Germany	2016	63		Conventional pacifier X physiological pacifier nonpacifier	Overjet Anterior open bite Overbite

[a]Interventional study

When breastfeeding versus bottle-feeding and its impact on mixed and permanent dentition malocclusion was investigated, a systematic review including only six studies concluded that there is nonconsistent evidence to support this association. [130].

Some methodological aspects contribute to the existed inconsistency among findings from different studies. The multiple forms of definition of malocclusion make difficult the standardization of malocclusion classification in epidemiological studies. Moreover, it is not uncommon to analyze malocclusion as an overall diagnosis, which may lead to confounding from other potentially unrelated malocclusion traits and obscure the underlying relationship. On the other hand, the classification of breastfeeding is challengeable and may impact the findings of the studies [131].

Breastfeeding may also have an indirect effect linked to the reduction of the risk of developing harmful oral habits related to certain types of malocclusion, such as anterior open bite, crossbite, and anteroposterior deviations in dental occlusion [32, 33].

In addition, breastfeeding has been suggested to be a protective factor for pediatric Obstructive Sleep Apnea (OSA) [132]. Pediatric OSA has been linked to some malocclusion traits. A protective association seems to exist, but caution should be exercised as only a moderate level of certainty is supported. At this time, it would be better not to imply such an association.

5.4.5 Preventable Diseases and Conditions Associated with Malocclusion

Dental caries has been associated with the presence of malocclusion in the mixed dentition of children in Romania [133] and permanent dentition in Hungarian adolescents [85]. Moreover, overbite was more likely to be found in Chinese children who have any experience of caries [134]. However, the relationship between the two oral conditions is not well established in deciduous dentition [135].

In addition to dental caries, other childhood health problems have been studied as risk factors for the presence of malocclusion. Some authors suggest a close relationship between the presence of malocclusions and the prevalence of mouth breathing and/or respiratory diseases due to changes in the physiological balance of growth. A systematic review concluded that Angle Class II, Division I is more prevalent in mouth breathing children [136]. Moreover, a study comprising

more than 3000 children found mouth breathing as a risk factor for increased overjet, reduced overjet, anterior or posterior crossbite, open bite, and displacement of contact points [137].

Pediatric OSA is a multifactorial disease that has been linked to specific craniofacial characteristics [138]. It is not currently clear if certain craniofacial features predispose the individuals to OSA or if OSA in growing children alters craniofacial features [139]. Currently, research is underway to better identify a subgroup of children for whom interception of altered craniofacial characteristics may prevent the development or further evolution of OSA. What seems to be clear is that not all pediatric OSA cases do have specific craniofacial characteristics and that not all OSA cases would clearly benefit from orthodontic intervention. Due to normal craniofacial growth and development (increase in the dimensions of the skeletal frame surrounding the upper airways) and normal shrinkage of lymphoid tissues (the most likely cause of pediatric OSA), sometimes watchful follow-up may be the best management approach in some instances [140].

5.5 Impact of Malocclusion on Individuals' Quality of Life

In health sciences, quality of life (QoL) specifically quantifies several aspects of the impact of health conditions on daily life; therefore, it is more precisely named health-related quality of life (HRQoL) [141]. Even more specific is the concept of oral health–related quality of life (OHRQoL) that describes how craniofacial disorders influence individuals' well-being [142].

During the last 30 years, studies on the association between the presence of malocclusion or orthodontic treatment need and OHRQoL have been subject of interest in different countries, especially among those countries that have some level of public sponsored support for some level of orthodontic treatment. More and more, there is the need to justify utilization of those funds where the maximum benefits are ripening. The potentially harmful impact of malocclusion on physical, psychological, and social characteristics of the individuals drives the need of such studies as well as the adoption of several OHRQoL tools to assess the portrayed association at a population level. Summarized information of the available studies allows us to establish a global picture on the level of evidence of the impact of malocclusion on OHRQoL. At least five systematic reviews (SRs) addressing this subject have been published in the scientific literature as of October 2018 (◘ Table 5.6). They were published between 2008 and 2016, and it must be noted that they differ in respect to the target population and assessed outcomes (quality-of-life indicators) apart from the investigated period.

Children and adolescents were the target population in three of SRs [125, 143, 144], adults aged 15 years or over in one [145] and subjects with ages varying from childhood to adulthood in one study only [145]. Studies comprising children and adolescents had similar aims and searched strategy; however, in one SR [144], they measured the impact of orthodontic treatment or having a before–after treatment design but used only the information on the untreated control groups. The most significant impact of malocclusion on children and adolescent's OHRQoL seems to be related to emotional and social well-being dimensions rather than in functional dimensions [125, 143]. Discomfort in laughing, limited social interaction, and reduced self-esteem were more likely to be affected than problems related to speaking and eating; moreover, the impact of malocclusion on OHRQoL increases with age with no association being found between malocclusion and quality-of-life level among young children [144].

In contrast, the SR including populations from different age groups [146] found in both generic (HRQoL) and oral health-specific (OHRQoL) instruments a moderate association between malocclusion/orthodontic treatment need and the overall score of QoL, regardless of the QoL instrument employed. The inclusion of generic instruments to measure QoL in this SR placed malocclusion in a broader perspective enabling to establish the impact of this specific oral health condition concerning more general health dimensions, and it also allowed for comparisons with diseases of different nature. The SR including studies conducted with older adolescents and adults contribute to elucidate if the association between malocclusion or its associated treatment with OHRQoL changes or persists along the lifetime [145]. When using the short version of a specific OHRQoL instrument (OHIP-14 – Oral Health Impact Profile), this SR showed that in general terms people without malocclusion had lower OHIP-14 scores (lower harmful impact) than those with malocclusion, however, with a significant level of heterogeneity between the investigated studies (◘ Table 5.6).

In general, heterogeneity due to OHRQoL measures used as well as because of variation in assessment methods for malocclusion partially explained differences between studies in all described SRs. It is highly likely that cultural and social environments may also have an essential role in the way how people interpret OHRQoL and perceived malocclusion. The low quality of the available studies and the lack of inclusion of potential confounders in most of the studies such as age, sex, and socioeconomic aspects are still gapping that need to be closed in future related studies.

Table 5.6 Association between malocclusion/orthodontic treatment need and OHRQoL based on systematic reviews

Authors/year	Source/period	Study population	Studies (*n*)	Malocclusion (s)	OHRQoL	Findings
Barbosa and Gaviao 2008 [143]	Medline, ISI, Lilacs, Scielo – January 1995 to October 2007	Children 8–15 years old	7	None, slight, moderate, severe, overjet, IOTN, DAI	CPQ, COHIP, Child-OIDP	The most significant impact of malocclusion was in the psychosocial aspects. Only one study did not find an association despite the wide variation in OHRQoL indices used in the included studies. Some malocclusions may not affect OHRQoL
Liu et al. 2009 [146]	Medline, EMBASE, CENTRAL, CINAHL – January 1960 to December 2007	8–30 years old	23	DAI, IOTN, subjective DFI, ICON, PAR, severity score, overjet, spacing, Class II division	$CPQ_{11–14}$, COHIP WHOQOL-BRIEF, SF36, SOHSI, orthognathic quality-of-life questionnaire, OIDP, child OIDP, PIDAQ, Oral Aesthetic Subjective Impact Scale Psychological scales	A modest association between malocclusion and HRQoL, studies are very heterogeneous for both malocclusion and HRQoL assessments. Level of evidence considered relatively low
Dimberg et al. 2015 [125]	Medline, EMBASE, PsycINFO, CINAHL, Cochrane Library – 1960 to January 2014	Children and adolescents (6–18 years old)	6	DAI, IOTN	$CPQ_{11–14}$, OHIP-14, OIDP	Severe malocclusion negatively impacts OHRQoL, predominantly in the emotional and social dimensions. Studies assessed were predominantly from Brazil, which may influence the results due to cultural bias
Kragt et al. [144]	Medline, OvidSP, EMBASE, Web-of-Sciences, Cochrane central, PsycINFO, OvidSP, Scopus, CINAHL, Google Scholar – until September 2015	Mean age <18 years old	40	DAI, IOTN, anterior trait, Angle's classification, presence/absence, hypodontia, DAI/PAR, DAI/any malocclusion	ECOHIS, $CPQ_{8–10}$, OHIP-14, COHIP, CPQ_{11-14}, CS-OIDP, OASIS, C-OIDP	There is a small impact of malocclusion on OHRQoL in children, but this effect increases by age and is modified by cultural aspects. Dichotomous and continuous data were analyzed, and the size of the impact was estimated (meta-analysis)
Andiappan et al. [145]	Medline, PubMed, EMBASE – until November 2013	≥15 years of age	11	DAI, IOTN, complaints, Classes II and III malocclusion, dentofacial deformity	OHIP, OHIP-14	People without malocclusion/ orthodontic treatment need had lower OHIP-14 scores compared with their counterparts. High-quality studies were analyzed. The authors identified a high level of heterogeneity among studies and publication bias

Table 5.7 Malocclusion/orthodontic treatment need and OHRQoL: country, age group, study design, sample size, and participants

Author(s)/year	Country	Age group (years)	Type of study	Sample size	Representativeness
Tuchtenhagen et al. 2016 [152]	Brazil	12	Cross-sectional	1134	Schoolchildren
Araki et al. 2017 [153]	Mongolia	10–16	Cross-sectional	420	Two public schools
Da Cunha et al. 2017 [148]	Brazil	15–19	Cross-sectional	5402	Population-based study
Martins et al. 2017 [149]	Brazil	8–10	Case–control study nested in a cross-sectional study	546	Schoolchildren
Kavaliauskiene et al. 2018 [154]	Lithuania	11–18	Cross-sectional	911	Public schools
Fabian et al. 2018 [151]	Germany	9–15	Cross-sectional nested in a cohort study	784	Population-based study
Sun et al. 2018 [150]	Hong Kong	18	Cross-sectional	300	School-based study
Anthony et al. 2018 [147]	Zambia	12–14	Cross-sectional	384	Schoolchildren

Summary of the studies

A search for original articles after reviewing the SRs mentioned above was conducted in PubMed from January 1, 2016, to October 27, 2018, limited to articles published in the English language. The search strategy including only the terms "quality of life" AND "malocclusion" generated 148 new publications from that 40 new population-based and school-based studies were found. Those population-representative studies comprised subjects living in low- and middle-income countries such as Zambia [147] and Brazil [148, 149] as well as in high-income countries such as Hong Kong [150] and Germany [151]. It must be noted that the cross-sectional design remains the primary research approach when focusing mainly on children and adolescents (Table 5.7). Malocclusion was investigated considering individual malocclusion traits such the presence of overbite [151] or overjet [148, 151] or more comprehensive occlusal indices such as DAI [147, 150, 152], ICON [150], and IOTN [150, 153, 154]. These indices include specific malocclusion traits which may be or not be related to specific domains of the OHRQoL and, therefore, may differently impact QoL [144] (Table 5.8). In addition, in some cases, the validation of the utilized tool was not reported. Hence, the instruments may not have properly measured the intended outcome.

Overall, findings from these studies reinforce the previous published SR's conclusions where greater scores of OHRQoL indices were associated with more severe malocclusion traits. From the OHRQoL indices, it appears that emotional and social well-being were the most common dimensions affected by the presence of malocclusion traits [151–154] with increased overjet affecting functional aspects emphasized in only one study [151]. The absence of classic confounders such as sex and socioeconomic position and other more specifics confounders such as access to orthodontic treatment and the evaluation of other oral conditions are limitations pointed out by several authors [149, 151] (Table 5.8). It is also important to be aware that this synthesis did not consider assessment of risk of bias among the considered studies. Nevertheless, the identified trends do provide an overview of our current understanding of this topic.

In summary, despite looking at different malocclusion traits and employing a broad range of HRQoL instruments, studies have shown a consistently negative impact of malocclusion on day-to-day life events among children and adolescents. It must be emphasized that this impact is more likely circumscribed to the emotional and social well-being dimensions and not likely to the functional dimension. More attention is necessary for incorporating study designs which would allow the investigation of this impact throughout the course of the adolescents' life. Moreover, the impact of malocclusion on the adults' quality of life could be better explored looking at the implications for public health action.

Table 5.8 Malocclusion/orthodontic treatment need and OHRQoL: type of malocclusion, outcome, confounders, and main findings and limitations

Author(s)/year	Malocclusion	OHRQoL	Confounders	Main findings	Limitations
Araki et al. 2017 [153]	IOTN index	Child Perceptions Questionnaire (CPQ)	Age, sex, family income, dental caries, frequency of toothbrushing	1. Overall, no association between malocclusion and CPQ 2. Increased overjet positively associated with oral symptoms (coef. 0.66, 95% CI [0.14–1.19]) and social well-being (coef. 0.50, 95% CI [0.06–0.93]) 3. Deep bite	Sample bias; IOTN index – only the worst occlusal traits recorded
Kavaliauskiene et al. 2018 [154]	IOTN – DHC index	Child Perceptions Questionnaire (CPQ)	Age, gender, family affluence scale (car and home computer ownership, own bedroom, and traveling on holidays), orthodontic treatment	Worst IOTN grade affected emotional well-being (RSSM 1.14 [95% CI 1.05–1.24]), was higher in girls (RSSM 1.67 [95% CI 1.36–2.05]) and among less affluent children (RSSM 0.7. [95% CI 0.56–0.93]); and social well-being (RSSM 1.19 [95% CI, 1.05–1.35])	IOTN index – only the worst occlusal traits recorded; possible selection bias
Tuchtenhagen et al. 2016 [152]	DAI	CPQ_{11-14}	Dental trauma, socioeconomic status	Severe malocclusion associated with high means of CPQ_{11-14} overall score. Social and emotional well-being domains were the most affected	Study design and absence of evaluation of other children characteristics
Fabian et al. 2018 [151]	Overbite Overjet	Child Perceptions Questionnaire (CPQ) – Germany	Age, gender, orthodontic treatment	Overjet ≥6 mm increase the CPQ summary score (6.1 [95% CI 1.0–11.2]), functional limitations (1.9 [95% CI [0.2–3.5]), emotional being (2.2 [95% CI 0.6–3.8]), and social well-being (1.8 [95% CI 0.1–3.8]).	Residual confounding lack of other (oral conditions)
Sun et al. 2018 [150]	IOTN, DAI, ICON, and PAR indexes	OHIP-14	Gender, father's education, household income, periodontal status, caries experience, and orthodontic treatment need	Worst experience in the general score of the OHIP-14 was associated with IOTN (AC), borderline orthodontic need (2.0 [95% CI 1.0–3.8]), severe DAI malocclusion (1.8 [95% CI 1.1–3.0]), treatment need according to ICON (2.1 [95%1.3–3.2]), and PAR malocclusion 91.9 [95% CI 1.3–3.0]) when compared with the best categories of each index. Subjects with malocclusion had a higher score than those without malocclusion (ICON and PAR indexes) in all subscales of OHIP-14	Study design
Anthony et al. 2018 [147]	DAI index	COHIP-SF19	Age, sex	The children with crowding (3.93 [95% CI (1.46–10.60]), diastema (3.96 [95% CI (1.31–11.97]), and spacing (4.32 [95% CI (1.38–13.55]) were more likely to report higher impact on OHRQoL than the children without these malocclusions	Lack of external validity and other potential confounders (dental caries and periodontal disease)
Da Cunha et al. 2017 [148]	Overjet, vertical open bite	OIDP	Gender, sex, skin color, family income, toothache, gingival bleeding, dental calculus	Overjet ≥6 mm (OR 1.68 [95% CI 1.15–2.45]) negatively affected QoL	Lack of training and calibration and information bias
Martins et al. 2017 [149]		CPQ_{8-10}	Dental caries and traumatic injuries	No association	Lack of classical confounders

Summary of the studies

5.6 Final Considerations

The range of aspects considered during the evaluation of the individual's occlusal conditions depicted on the epidemiological studies varies significantly, as very different characteristics are considered that make comparative analyses challenging. Moreover, the use of clinical criteria in epidemiological studies is complex, making replication and reproducibility of significant clinical aspects difficult in field conditions.

The use of indices that consider biologically (anatomical or functional) or perceived attributes (quality of life, need for treatment) is further complicated by diagnostic subjectivity from both the professional (the indication of orthodontic treatment) and the individual examined (the perceived need or desire for orthodontic treatment). Hence, a clear dividing line between normative and subjective evaluation has little practical significance. Researchers emphasize that decision-making for orthodontic treatment should be a joint effort between health-care providers and those under orthodontic assessment. Ideally, this could be achieved through the evaluation of both a combination of normative and subjective characteristics. Some malocclusion indicators include components of normative diagnosis, together with subjective data, in which cultural aspects are considered in the evaluation of an acceptable occlusion, either under the aesthetic, emotional, functional, or social perception. Studies that included such components for malocclusion evaluation suggest that some occlusal deviations may be acceptable from a social judgment point of view and in contrast to the health professional's perspective. This may support the need to proper validation of any given index in the context of the specific population that is being assessed. On the other hand, conditions involving aesthetic impairment such as anterior dental crowding, anterior diastema, and anterior superior overjet are associated with individuals who consider themselves less attractive and with less opportunity for professional success. Moreover, an unfavorable dentofacial appearance can discriminate the individuals affected by these disorders, in their personal interrelationship both within the working environment and at school, reducing their life chances.

Given the historical limitation of access to resources to facilitate a therapeutic approach to malocclusion worldwide, a preventive approach could be strengthened with the appropriate use of epidemiological tools. This demands not only the description of quantitative aspects of the distribution of cases but also the identification and evaluation of risk factors underlined in this chapter. The use of a pacifier, the lack of breastfeeding, early weaning, the presence of some deviations of physical growth, and some systemic conditions could be addressed early to avoid the development of more complex malocclusions.

Nevertheless, malocclusions can be considered as a public health problem, since they present high prevalence, the possibility of prevention and treatment, and affect the quality of life of individuals. The estimation of the impact of malocclusion and the identification of which occlusal traits mostly affect individuals physically and emotionally would allow a more precise definition of malocclusion as a public health problem, thus better directing resources for its prevention and treatment.

Point of Emphasis

- For certain adults, adolescents, and children, malocclusion may impact their life with potential consequences on their emotional and social well-being, aesthetic, and functional aspects.
- Due to a wide range of different criteria for recording the occlusal condition, comparisons between findings from different epidemiological surveys are challenging.
- The inclusion of normative and subjective aspects in malocclusion indicators in future research might help to close the gap between health-care providers' opinion and the self-perception of malocclusion of a determined population.
- A preventive approach could be strengthened with the appropriate use of epidemiological tools. This helps the early identification of risk factors for some malocclusions, such as the use of a pacifier, the lack of breastfeeding, early weaning, and the presence of some deviations of physical growth and some systemic conditions.

References

1. Frazao P, Narvai PC, Latorre Mdo R, Castellanos RA. Are severe occlusal problems more frequent in permanent than deciduous dentition? Rev Saúde Pública. 2004;38(2):247–54.
2. Davies SJ, Gray RM, Sandler PJ, et al. Orthodontics and occlusion. Br Dent J. 2001;191:539–42.
3. Proffit WR, Fields HW, Larson B, Sarver DM. Contemporary orthodontics. Saint Louis: C. V. Mosby Elsevier; 2018.
4. Peres KG, Barros AJD, Anselmo L, Peres MA, Barros FC. Does malocclusion influence the adolescent's satisfaction with appearance? A cross-sectional study nested in a Brazilian birth cohort. Community Dent Oral Epidemiol. 2008;36:137–43.
5. Bernabe E, Sheiham A, de Oliveira CM. Impacts on daily performances attributed to malocclusions by British adolescents. J Oral Rehabil. 2009;36:26–31.
6. Dimberg L, Bondemark L, Söderfeldt B, Lennartsson B. Prevalence of malocclusion traits and sucking habits among 3-year-old children. Swed Dent J. 2010;34(1):35–42.

7. Masood M, Suominen AL, Pietila T, Lahti S. Malocclusion traits and oral health-related quality of life in Finnish adults. Community Dent Oral Epidemiol. 2017;45(2):178–88.
8. Angle EH. Classification of malocclusion. Dent Cosmos. 1899;41:248–64.
9. Dewey M. Classification of malocclusion. Am J Orthod. 1915;1:133–47.
10. Simon PW. Grundzuge einer systematischen Diagnostik der Gebiss-Anomalien. Berlin: Hermann Meusser; 1922.
11. Ackermann JL, Proffit WR. The characteristics of malocclusion: a modern approach to classification and diagnosis. Am J Orthod. 1969;56:443–54.
12. Andrews LF. The six keys to normal occlusion. Am J Orthod Dentofac Orthoped. 1972;62:296–309.
13. American Board of Orthodontic. https://www.americanboardortho.com/media/1189/discrepancy_index_scoring_system.pdf. Accessed 5 Feb 2019.
14. Daly B, Watt R, Batchelor P, Treasure E. Overview of epidemiology. In: Essential dental public health. Oxford: University Press; 2002. p. 79–80.
15. Brook PH, Shaw WC. The development of an index of orthodontic treatment priority. Eur J Orthod. 1989;11(3):309–20.
16. Richmond S, Shaw WC, Roberts CT, Andrews M. The PAR Index (Peer Assessment Rating): methods to determine outcome of orthodontic treatment in terms of improvement and standards. Eur J Orthod. 1992;14(3):180–7.
17. Jenny J, Cons NC, Kohout FJ, Jakobsen J. Predicting handicapping malocclusion using the Dental Aesthetic Index (DAI). Int Dent J. 1993;43(2):128–32.
18. Daniels C, Richmond S. The development of the index of complexity, outcome and need (ICON). J Orthod. 2000;27(2):149–62. Erratum in: J Orthod. 2002;29(1):81.
19. Grainger RM. The orthodontic treatment priority index. Public Health Service Publication no. 1000 (Vital and Health Statistics) Series 2, No. 25. Washington DC: National Center for Health Statistics; 1967.
20. Dracker HL. Handicapping labio-lingual deviations: a propose index for public health purposes. Am J Orthod. 1960;46(4):295–305.
21. Bjork A, Helm S. Need for orthodontic treatment as reflected in the prevalence of malocclusion in various ethnic groups. Acta Odontol Scand. 1964;22:27–41.
22. Foster TD, Hamilton MC. Occlusion in the primary dentition: study of children at 2 ½ to 3 years of age. Br Dent J. 1969;126(2):76–81.
23. Summers CJ. The occlusal index: a system for identifying and scoring occlusal disorders. Am J Orthod. 1971;59(6):552–67.
24. Bezroukov V, Freer TJ, Helm S, Kalamkarov H, Sardo Infirri J, Solow B. Basic methods for recording occlusal traits. Bull World Health Organ. 1979;57(6):955–61.
25. World Health Organization. Oral health surveys: basic methods. 3rd ed. Geneva: WHO; 1987.
26. Chiavaro A. Malocclusion of temporary teeth. Int J Orthod. 1915;1(4):171–9.
27. Humphreys HF, Leighton BC. A survey of antero-posterior abnormalities of the jaws in children between the ages of 2 and 5 1/2 years of age. Br Dent J. 1950;88(1):3–15.
28. Almeida ER, Narvai PC, Frazão P, Pinto ACG. Revised criteria for the assessment and interpretation of occlusal deviations in the deciduous dentition: a public health perspective. Cad de Saúde Pública. 2008;24:897–904.
29. Shen L, He F, Zhang C, Jiang H, Wang J. Prevalence of malocclusion in primary dentition in mainland China, 1988-2017: a systematic review and meta-analysis. Sci Rep. 2018;8(1):4716.
30. Thilander B, Pena L, Infante C, Parada SS, de Mayorga C. Prevalence of malocclusion and orthodontic treatment need in children and adolescents in Bogota, Colombia. An epidemiological study related to different stages of dental development. Eur J Orthod. 2001;23(2):153–67.
31. Katz CR, Rosenblatt A, Gondim PP. Nonnutritive sucking habits in Brazilian children: effects on deciduous dentition and relationship with facial morphology. Am J Orthod Dentofac Orthop. 2004;126(1):53–7.
32. Peres KG, Latorre MRDO, Sheiham A, Peres MA, Victora CG, Barros FC. Social and biological early life influences on the prevalence of open bite in Brazilian 6-year-olds. Int J Paediatr Dent. 2007;17:41–9.
33. Peres KG, Barros AJD, Peres MA, Victora CM. Effects of breastfeeding and sucking habits on malocclusion in a birth cohort study. Rev Saude Publica. 2007;41:343–50.
34. Batwala V, Mulogo EM, Arubaku W. Oral health status of school children in Mbarara, Uganda. Afr Health Sci. 2007;7(4):233–8.
35. Grabowski R, Stahl F, Gaebel M, Kundt G. [Relationship between occlusal findings and orofacial myofunctional status in primary and mixed dentition. Part I: prevalence of malocclusions]. J Orofac Orthop. 2007;68(1):26–37.
36. Silva Filho OG, Santamaria M Jr, Capelozza Filho L. Epidemiology of posterior crossbite in the primary dentition. J Clin Pediatr Dent Fall. 2007;32(1):73–8.
37. Hebling SR, Cortellazzi KL, Tagliaferro EP, Hebling E, Ambrosano GM, Meneghim MC, Pereira AC. Relationship between malocclusion and behavioral, demographic and socioeconomic variables: a cross-sectional study of 5-year-olds. J Clin Pediatr Dent. 2008;33(1):75–9.
38. Macena MC, Katz CR, Rosenblatt A. Prevalence of a posterior crossbite and sucking habits in Brazilian children aged 18-59 months. Eur J Orthod. 2009;31(4):357–61.
39. Berneburg M, Zeyher C, Merkle T, Möller M, Schaupp E, Göz G. Orthodontic findings in 4- to 6-year-old kindergarten children from Southwest Germany. J Orofac Orthop. 2010;71(3):174–86.
40. Bhayya DP, Shyagali TR. Gender influence on occlusal characteristics of primary dentition in 4- to 6-year-old children of Bagalkot City, India. Oral Health Prev Dent. 2011;9(1):17–27.
41. Carvalho AC, Viegas CM, Scarpelli AC, Fereira FM, Pordeus IA, Paiva SM. Prevalence of malocclusion in primary dentition of a population-based sample of Brazilian preschool children. Eur J Paediatr Dent. 2011;12:107–11.
42. Romero CC, Scavone-Junior H, Garib DG, Cotrim-Ferreira FA, Ferreira RI. Breastfeeding and non-nutritive sucking patterns related to the prevalence of anterior open bite in primary dentition. J Appl Oral Sci. 2011;19(2):161–8.
43. Marquezan M, Marquezan M, Faraco-Junior IM, Feldens CA, Kramer PF, Ferreira SH. Association between occlusal anomalies and dental caries in 3- to 5 year-old Brazilian children. J Orthod. 2011;38(1):8–14.
44. Vasconcelos FM, Massoni AC, Heimer MV, Ferreira AM, Katz CR, Rosenblatt A. Non-nutritive sucking habits, anterior open bite and associated factors in Brazilian children aged 30-59 months. Braz Dent J. 2011;22(2):140–5.
45. Seemann J, Kundt G, Stahl de Castrillon F. Relationship between occlusal findings and orofacial myofunctional status in primary and mixed dentition: part IV: interrelation between space conditions and orofacial dysfunctions. J Orofac Orthop. 2011;72(1):21–32.
46. Urzal V, Braga AC, Ferreira AP. The prevalence of anterior open bite in Portuguese children during deciduous and mixed dentition – correlations for a prevention strategy. Int Orthod. 2013;11(1):93–103.
47. Baral P, Budathoki P, Bhuju KG, Koirala B. Prevalence of occlusal traits in the deciduous dentition of children of Kaski District, Nepal. JNMA J Nepal Med Assoc. 2014;52(195):862–5.

48. Sousa RV, Pinto-Monteiro AKA, Martins CC, Granville-Garcia AF, Paiva SM. Malocclusion and socioeconomic indicators in primary dentition. Braz Oral Res. 2014;28(1):54–60.
49. Normando TS, Barroso RF, Normando D. Influence of the socioeconomic status on the prevalence of malocclusion in the primary dentition. Dental Press J Orthod. 2015;20(1):74–8.
50. Souza BS, Bichara LM, Guerreiro JF, Quintão CCA, David ND. Occlusal and facial features in Amazon indigenous: an insight into the role of genetics and environment in the etiology dental malocclusion. Arch Oral Biol. 2015;60:1177–86.
51. Shavi GR, Hiremath NV, Shukla R, Bali PK, Jain SK, Ajagannanavar SL. Prevalence of spaced and non-spaced dentition and occlusal relationship of primary dentition and its relation to malocclusion in school children of Davangere. J Int Oral Health. 2015;7(9):75–8.
52. Zhou Z, Liu F, Shen S, Shang L, Shang L, Wang X. Prevalence of and factors affecting malocclusion in primary dentition among children in Xi'an, China. BMC Oral Health. 2016;16(1):91.
53. Newman GV, Newmark NJ. Prevalence of malocclusion in children six to fourteen years of age and treatment in preventable cases. J Am Dent Assoc. 1956;52(5):566–75.
54. Johnson M, Harkness M. Prevalence of malocclusion and orthodontic treatment need in 10-year-old New Zealand children. Aust Orthod J. 2000;16(1):1–8.
55. Keski-Nisula K, Lehto R, Lusa V, Keski-Nisula L, Varrela J. Occurrence of malocclusion and need of orthodontic treatment in early mixed dentition. Am J Orthod Dentofac Orthop. 2003;124(6):631–8.
56. Tausche E, Luck O, Harzer W. Prevalence of malocclusions in the early mixed dentition and orthodontic treatment need. Eur J Orthod. 2004;26(3):237–44.
57. Glasl B, Ludwig B, Schopf P. Prevalence and development of KIG-relevant symptoms in primary school students from Frankfurt am Main. J Orofac Orthop. 2006;67(6):414–23.
58. Perinetti G, Cordella C, Pellegrini F, Esposito P. The prevalence of malocclusal traits and their correlations in mixed dentition children: results from the Italian OHSAR Survey. Oral Health Prev Dent. 2008;6(2):119–29.
59. Grando G, Young AA, Vedovello Filho M, Vedovello SA, Ramirez-Yañez GO. Prevalence of malocclusions in a young Brazilian population. Int J Orthod Milwaukee. 2008;19(2):13–6.
60. Dias PF, Gleiser R. Orthodontic treatment need in a group of 9-12-year-old Brazilian schoolchildren. Braz Oral Res. 2009;23(2):182–9.
61. Martins MG, Lima KC. Prevalence of malocclusions in 10- to 12-year-old schoolchildren in Ceará, Brazil. Oral Health Prev Dent. 2009;7(3):217–23.
62. Dimberg L, Lennartsson B, Söderfeldt B, Bondemark L. Malocclusions in children at 3 and 7 years of age: a longitudinal study. Eur J Orthod. 2013;35(1):131–7.
63. Grippaudo C, Pantanali F, Paolantonio EG, Saulle R, Latorre G, Deli R. Orthodontic treatment timing in growing patients. Eur J Paediatr Dent. 2013;14(3):231–6.
64. Shalish M, Gal A, Brin I, Zini A, Ben-Bassat Y. Prevalence of dental features that indicate a need for early orthodontic treatment. Eur J Orthod. 2013;35(4):454–9.
65. Evensen JP, Øgaard B. Are malocclusions more prevalent and severe now? A comparative study of medieval skulls from Norway. Am J Orthod Dentofac Orthop. 2007;131(6):710–6.
66. Fudvoye J, Parent AS. Secular trends in growth. Ann Endocrinol (Paris). 2017;78(2):88–91.
67. Brin I, Zwilling-Sellam O, Harari D, Koyoumdjisky E, Ben-Bassat Y. Does secular trends exist in the distribution of occlusal patterns? Angle Orthod. 1998;68(1):81–4.
68. Tapsoba H, Bakayoko-Ly R. Oral health status of 12-year-old schoolchildren in the province of Kadiogo, Burkina Faso. Community Dent Health. 2000;17(1):38–40.
69. Ciuffolo F, Manzoli L, D'Attilio M, Tecco S, Muratore F, Festa F, Romano F. Prevalence and distribution by gender of occlusal characteristics in a sample of Italian secondary school students: a cross-sectional study. Eur J Orthod. 2005;27(6):601–6.
70. Bilgic F, Gelgor IE, Celebi AA. Malocclusion prevalence and orthodontic treatment need in central Anatolian adolescents compared to European and other nations' adolescents. Dental Press J Orthod. 2015;20(6):75–81.
71. Laganà G, Masucci C, Fabi F, Bollero P, Cozza P. Prevalence of malocclusions, oral habits and orthodontic treatment need in a 7- to 15-year-old schoolchildren population in Tirana. Prog Orthod. 2013;14:12.
72. Al-Azemi R, Artun J. Orthodontic treatment need in adolescent Kuwaitis: prevalence, severity and manpower requirements. Med Princ Pract. 2010;19(5):348–54.
73. Mtaya M, Brudvik P, Astrøm AN. Prevalence of malocclusion and its relationship with socio-demographic factors, dental caries, and oral hygiene in 12- to 14-year-old Tanzanian schoolchildren. Eur J Orthod. 2009;31(5):467–76.
74. Bhardwaj VK, Veeresha KL, Sharma KR. Prevalence of malocclusion and orthodontic treatment needs among 16 and 17 year-old school-going children in Shimla city, Himachal Pradesh. Indian J Dent Res. 2011;22(4):556–60.
75. Anosike AN, Sanu OO, da Costa OO. Malocclusion and its impact on quality of life of school children in Nigeria. West Afr J Med. 2010;29(6):417–24.
76. Szöke A, Petersen PE. Evidence for dental caries decline among children in an East European country (Hungary). Community Dent Oral Epidemiol. 2000;28(2):155–60.
77. Goel P, Sequeira P, Peter S. Prevalence of dental disease amongst 5-6 and 12-13-year-old school children of Puttur municipality, Karnataka State-India. J Indian Soc Pedod Prev Dent. 2000;18(1):11–7.
78. Esa R, Razak IA, Allister JH. Epidemiology of malocclusion and orthodontic treatment need of 12-13-year-old Malaysian schoolchildren. Community Dent Health. 2001;18:31–6.
79. Onyeaso CO, Isiekwe MC. Oral habits in the primary and mixed dentitions of some Nigerian children: a longitudinal study. Oral Health Prev Dent. 2008;6(3):185–90.
80. Baca-Garcia A, Bravo M, Baca P, Baca A, Junco P. Malocclusions and orthodontic treatment needs in a group of Spanish adolescents using the Dental Aesthetic Index. Int Dent J. 2004;54:138–42.
81. Alkhatib MN, Bedi R, Foster C, Jopanputra P, Allan S. Ethnic variations in orthodontic treatment need in London schoolchildren. BMC Oral Health. 2005;5:8.
82. Behbehani F, et al. Prevalence and severity of malocclusion in adolescent Kuwaitis. Med Princ Pract. 2005;14(6):390–5.
83. Van Wyk PJ, Drummond RJ. Orthodontic status and treatment need of 12-year-old children in South Africa using the Dental Aesthetic Index. SADJ. 2005;60(8):334–6.
84. Abu Alhaija ES, Al-Khateeb SN, Al-Nimri KS. Prevalence of malocclusion in 13-15-year-old North Jordanian school children. Community Dent Health. 2005;22(4):266–71.
85. Gábris K, Márton S, Madléna M. Prevalence of malocclusions in Hungarian adolescents. Eur J Orthod. 2006;28(5):467–70.
86. Frazão P, Narvai PC. Socio-environmental factors associated with dental occlusion in adolescents. Am J Orthod Dentofac Orthop. 2006;129:809–16.
87. Rwakatema DS, Ng'ang'a PM, Kemoli AM. Orthodontic treatment needs among 12-15 year-olds in Moshi, Tanzania. East Afr Med J. 2007;84(5):226–32.

88. Dhar V, Jain A, Van Dyke TE, Kohli A. Prevalence of gingival diseases, malocclusion and fluorosis in school-going children of rural areas in Udaipur district. J Indian Soc Pedod Prev Dent. 2007;25(2):103–5.
89. Manzanera D, Montiel-Company JM, Almerich-Silla JM, Gandía JL. Orthodontic treatment need in Spanish schoolchildren: an epidemiological study using the Index of Orthodontic Treatment Need. Eur J Orthod. 2009;31(2):180–3.
90. Shivakumar KM, Chandu GN, Reddy S. Prevalence of malocclusion and orthodontic treatment needs among middle and high school children of Davangere city, India by using Dental Aesthetic Index. J Indian Soc Pedod Prev Dent. 2009;27:211–8.
91. Borzabadi-Farahani A, Borzabadi-Farahani A, Eslamipour F. Malocclusion and occlusal traits in an urban Iranian population. An epidemiological study of 11- to 14-year-old children. Eur J Orthod. 2009;31(5):477–84.
92. Eslamipour F, Borzabadi-Farahani A, Asgari I. Assessment of orthodontic treatment need in 11- to 20-year-old urban Iranian children using the Dental Aesthetic Index (DAI). World J Orthod. 2010;11(4):e125–32.
93. Nagarajan S, Pushpanjali K. The relationship of malocclusion as assessed by the Dental Aesthetic Index (DAI) with perceptions of aesthetics, function, speech and treatment needs among 14- to 15-year-old schoolchildren of Bangalore, India. Oral Health Prev Dent. 2010;8(3):221–8.
94. Murshid ZA, Amin HE, Al-Nowaiser AM. Distribution of certain types of occlusal anomalies among Saudi Arabian adolescents in Jeddah city. Community Dent Health. 2010;27(4):238–41.
95. Peres MA, Barros AJ, Peres KG, Araújo CL, Menezes AM, Hallal PC, Victora CG. Oral health follow-up studies in the 1993 Pelotas (Brazil) birth cohort study: methodology and principal results. Cad Saude Publica. 2010;26(10):1990–9.
96. Singh A, Purohit B, Sequeira P, Acharya S, Bhat M. Malocclusion and orthodontic treatment need measured by the dental aesthetic index and its association with dental caries in Indian schoolchildren. Community Dent Health. 2011;28(4):313–6.
97. Phaphe S, Kallur R, Vaz A, Gajapurada J, Raddy S, Mattigatti S. To determine the prevalence rate of malocclusion among 12 to 14-year-old schoolchildren of urban Indian population (Bagalkot). J Contemp Dent Pract. 2012;13(3):316–21.
98. Muasya MK, Ng'Ang'a M, Opinya GN, Macigo FG. Malocclusion and orthodontic treatment need among 12-15-year-old children in Nairobi. East Afr Med J. 2012;89(2):39–44.
99. Peres KG, Frazão P, Roncalli AG. [Epidemiological pattern of severe malocclusions in Brazilian adolescents]. Rev Saude Publica. 2013;47 Suppl 3:109–17.
100. Aikins EA, Onyeaso CO. Prevalence of malocclusion and occlusal traits among adolescents and young adults in Rivers State, Nigeria. Odontostomatol Trop. 2014;37(145):5–12.
101. Spalj S, Slaj M, Athanasiou AE, Govorko DK, Slaj M. The unmet orthodontic treatment needs of adolescents and influencing factors for not seeking orthodontic therapy. Coll Antropol. 2014;38 Suppl 2:173–80.
102. Silveira MF, Freire RS, Nepomuceno MO, Martins AM, Marcopito LF. Severity of malocclusion in adolescents: populational-based study in the north of Minas Gerais, Brazil. Rev Saúde Pública. 2016;50:11.
103. Goettems ML, Ourens M, Cosetti L, Lorenzo S, Álvarez-Vaz R, Celeste RK. Early-life socioeconomic status and malocclusion in adolescents and young adults in Uruguay. Cad Saude Publica. 2018;34(3):e00051017. 7.
104. Infante PF. Malocclusion in the deciduous dentition in white, black, and Apache Indian children. Angle Orthod. 1975; 45(3):213–8.
105. Wagner Y, Heinrich-Weltzien R. Occlusal characteristics in 3-year-old children – results of a birth cohort study. BMC Oral Health. 2015;15:94.
106. Meyers A, Hertzberg J. Bottle feeding and malocclusion: is there an association? Am J Orthod Dentofacial Orthop. 1988;93:149–52.
107. Kharbanda OP, Sidhu SS, Shukla DK, Sundaram KR. A study of the etiological factors associated with the development of malocclusion. J Clin Pediatr Dent. 1994;18(2):95–8.
108. Peres MA, de Oliveira Latorre Mdo R, Sheiham A, Peres KG, Barros FC, Hernandez PG, et al. Social and biological early life influences on severity of dental caries in children aged 6 years. Community Dent Oral Epidemiol. 2005;33:53–63.
109. Thomaz EBAF, Valença AMG. Associação entre déficit de peso e apinhamento na dentição decídua. J Pediatr. 2009;85(2):110–6.
110. Paulsson L, Bondemark L, Söderfeldt B. A systematic review of the consequences of premature birth on palatal morphology, dental occlusion, tooth-crown dimensions, and tooth maturity and eruption. Angle Orthod. 2004;74(2):269–79.
111. Germa A, Clément C, Weissenbach M, Heude B, Forhan A, Martin-Marchand L, Bonet M, Vital S, Kaminski M, Nabet C. Early risk factors for posterior crossbite and anterior open bite in the primary dentition. Angle Orthod. 2016;86(5):832–8.
112. Campos MPMS, Valença PAM, Silva GMD, Lima MC, Jamelli SR, Góes PSA. Influence of head and linear growth on the development of malocclusion at six years of age: a cohort study. Braz Oral Res. 2018;32:e98.
113. Alvarez JO, Caceda J, Woolley TW, Carley KW, Baiocchi N, Caravedo L, Navia JM. A longitudinal study of dental caries in the primary teeth of children who suffered from infant malnutrition. J Dent Res. 1993;72(12):1573–6.
114. Bastos JL, Peres MA, Peres KG, Barros AJD. Infant growth, development and tooth emergence patterns: a longitudinal study from birth to 6 years of age. Arch Oral Biol. 2007;52:598–606.
115. Gaur R, Kumar P. Effect of undernutrition on deciduous tooth emergence among Rajput children of Shimla District of Himachal Pradesh, India. Am J Phys Anthropol. 2012;148(1):54–61.
116. Levine RS. Briefing paper: oral aspects of dummy and digit sucking. Br Dent J. 1999;186(3):108.
117. Schmid KM, Kugler R, Nalabothu P, Bosch C, Verna C. The effect of pacifier sucking on orofacial structures: a systematic literature review. Prog Orthod. 2018;19:8.
118. Medeiros R, Ximenes M, Massignan C, Flores-Mir C, Vieira R, Porporatti AL, de Luca Canto G. Malocclusion prevention through the usage of an orthodontic pacifier compared to a conventional pacifier: a systematic review. Eur Arch Paediatr Dent. 2018;19(5):287–95.
119. Heimer MV, Tornisiello Katz CR, Rosenblatt A. Non-nutritive sucking habits, dental malocclusions, and facial morphology in Brazilian children: a longitudinal study. Eur J Orthod. 2008;30(6):580–5.
120. Duncan K, McNamara C, Ireland AJ, Sandy JR. Sucking habits in childhood and the effects on the primary dentition: findings of the Avon Longitudinal Study of Pregnancy and Childhood. Int J Paediatr Dent. 2008;18(3):178–88.
121. Moimaz SAS, Garbin AJI, Lima AMC, Saliba LFLO, Garbin CAS. Longitudinal study of habits leading to malocclusion development in childhood. BMC Oral Health. 2014;14:96.
122. Feres M, Abreu LG, Insabralde NM, de Almeida MR, Flores-Mir C. Effectiveness of the open-bite correction when managing deleterious oral habits in growing children and adolescents: a systematic review and meta-analysis. Eur J Orthod. 2017;39:31–42.

123. Warren JJ, Bishara SE, Steinbock KL, Yonezu T, Nowak AJ. Effects of oral habits' duration on dental characteristics in the primary dentition. J Am Dent Assoc. 2001;132:1685–93.
124. Doğramacı EJ, Rossi-Fedele G. Establishing the association between nonnutritive sucking behavior and malocclusions: a systematic review and meta-analysis. J Am Dent Assoc. 2016;147(12):926–934.e6.
125. Dimberg L, Arnup K, Bondemark L. The impact of malocclusion on the quality of life among children and adolescents: a systematic review of quantitative studies. Eur J Orthod. 2015;37(3):238–47.
126. Victora CG, Bahl R, Barros AJD, Franca GVA, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475–90.
127. Woolridge M. The "anatomy" of infant sucking. Midwifery. 1986;2(4):164–71.
128. Drane D. The effect of use of dummies and teats on orofacial development. Breastfeed Rev. 1996;4:59–64.
129. Peres KG, Cascaes AM, Nascimento GG, Victora CG. Effect of breastfeeding on malocclusion: a systematic review and meta-analysis. Acta Paediatr. 2015;104:54–61.
130. Abreu LC, Paiva SM, Pordeus IA, Martins CC. Breastfeeding, bottle feeding and risk of malocclusion in mixed and permanent dentitions: a systematic review. Braz Oral Res. 2016;30(1):e22.
131. Peres KG, Chaffee BW, Feldens CA, Flore-Mir C, Moynihan P, Rugg-Gunn A. Breastfeeding an oral health: evidence and methodological challenges. J Dent Res. 2018;97(3):251–8.
132. Ponce-Garcia C, Hernandez I, Major PW, Flores-Mir C. Association between breast feeding and pediatric sleep disordered breathing: a systematic review. Paediatr Perinat Epidemiol. 2017;31:348–62.
133. Cernei ER, Maxim DC, Zegan G. The study of the association of decay risk with malocclusions in mixed dentition at children from Northeast Romania. A transversal retrospective study. Rev Med Chir Soc Med Nat Iasi. 2016;120(4):932–41.
134. Caplin JL, Evans CA, Begole EA. The relationship between caries and malocclusion in Chinese migrant workers' children in Shanghai. Chin J Dent Res. 2015;18(2):103–10.
135. Al-Shahrani N, Al-Amri A, Hegazi F, Al-Rowis K, Al madani A, Hassan K. The prevalence of premature loss of primary teeth and its impact on malocclusion in the Eastern Province of Saudi Arabia. Acta Odontol Scand. 2015;73(7):1–6.
136. Fraga WS, Seixas VMS, Santos JCS, Paranhos LR, Cesar CP. Mouth breathing in children and its impact in dental malocclusion: a systematic review of observational studies. Minerva Stomatol. 2018;67(3):129–38.
137. Grippaudo C, Paolantonio EG, Antonini G, Saulle R, La Torre G, Deli R. Association between oral habits, mouth breathing and malocclusion. Acta Otorhinolaryngol Ital. 2016;36(5):386–94.
138. Flores-Mir C, Pizzatto J. Pediatric sleep disorder breathing – Some basic concepts pertinent to orthodontics. In: McNamara Jr JA, Shelgikar AV, editors. Sleep apnea: what every clinician and patient should know. Ann Arbor: Monograph 54, Craniofacial Growth Series, Department of Orthodontics and Pediatric Dentistry and Center for Human Growth and Development, The University of Michigan; 2018.
139. Flores-Mir C, Korayem M, Major MP, Witmans M, Major PW. Craniofacial morphology in children with obstructive sleep apnea syndromes: a systematic review & meta-analysis. J Am Dent Assoc. 2013;144:269–77.
140. Stark TR, Pozo-Alonso M, Daniels R, Camacho M. Pediatric considerations for dental sleep medicine. Sleep Med Clin. 2018;13:531–48.
141. World Health Organization (WHO). Study protocol for the World Health Organization project to develop a quality of life assessment instrument (WHOQOL). Qual Life Res. 1993;2(2):153–19.
142. Inglehart M, Bagramian R. Oral health-related quality of life. Chicago: Quintessence Publishing; 2002. p. 1–6. isbn:0-86715-421-7.
143. Barbosa TS, Gaviao MBD. Oral health-related quality of life in children: part II. Effects of clinical oral health status. A systematic review. Int J Dent Hyg. 2008;6:100–7.
144. Kragt L, Dhamo B, Wolvius EB, Omgkosuwito EM. The impact of malocclusions on oral health-related quality of life in children – a systematic review and meta-analysis. Clin Oral Investig. 2016;20:1881–94.
145. Andiappan M, Gao W, Bernabe E, Kandala NB, Donaldson AN. Malocclusion, orthodontic treatment, and the Oral Health Impact Profile (OHIP-14): systematic review and meta-analysis. Angle Orthod. 2015;85(3):493–500.
146. Liu Z, McGrath C, Hagg U. The impact of malocclusion/orthodontic treatment need on the quality of life a systematic review. Angle Orthod. 2009;79(3):585–91.
147. Anthony SN, Zimba K, Subramanian B. Impact of malocclusions on the oral health-related quality of life of early adolescents in Ndola, Zambia. Int J Dent. 2018;3:7920973.
148. Da Cunha IP, Pereira AC, Frias AC, Vieira V, Meneghin MC, Batista MJ, et al. Social vulnerability and factors associated with oral impact on daily performance among adolescents. Health Qual Life Outcomes. 2017;15:173.
149. Martins MT, Sardenberg F, Bendo CB, Abreu MH, Vale MP, Paiva SM, et al. Dental caries remains as the main oral condition with the greatest impact on children's quality of life. PLoS One. 2017;12(10):e0185365.
150. Sun L, Wong HM, McGrath CPJ. The factors that influence oral health-related quality of life in young adults. Health Qual Life Outcomes. 2018;16:187.
151. Fabian S, Gelbrich B, Hiemisch A, Kiess W, Hirsch, LIFE Child study team. Impact of overbite and overjet on oral health-related quality of LIFE of children and adolescents. J Orofac Orthop. 2018;79(1):29–38.
152. Tuchtenhagen S, Bresolin CR, Tomazoni F, da Rosa GN, Del Silva JP, Mendes FM, et al. The influence of normative and subjective oral health status on schoolchildren's happiness. BMC Oral Health. 2015;15:15.
153. Araki M, Yasuda Y, Ogawa T, Tumurkhuu T, Ganburged G, Bazar A, et al. Associations between malocclusion and oral health-related quality of life among Mongolian adolescents. Int J Environ Res Public Health. 2017;14(8):902.
154. Kavaliauskienė A, Šidlauskas A, Zaborskis A. Relationship between orthodontic treatment need and oral health-related quality of life among 11–18-year-old adolescents in Lithuania. Int J Environ Res Public Health. 2018;15(5):1012.

Further Reading

Andiappan M, Gao W, Bernabe E, Kandala NB, Donaldson AN. Malocclusion, orthodontic treatment, and the Oral Health Impact Profile (OHIP-14): systematic review and meta-analysis. Angle Orthod. 2015;85(3):493–500.
Flores-Mir C, Korayem M, Major MP, Witmans M, Major PW. Craniofacial morphology in children with obstructive sleep apnea syndromes: a systematic review & meta-analysis. J Am Dent Assoc. 2013;144:269–77.
Peres KG, Chaffee BW, Feldens CA, Flore-Mir C, Moynihan P, Rugg-Gunn A. Breastfeeding an oral health: evidence and methodological challenges. J Dent Res. 2018;97(3):251–8.

Orofacial Pain

Mario Vianna Vettore and Gabriela de Almeida Lamarca

Contents

6.1 Introduction – 108

6.2 Definition of Pain and Orofacial Pain – 109

6.3 Diagnosis and Classification of Orofacial Pain – 109

6.4 Measures and Instruments of Orofacial Pain – 111

6.5 Epidemiology of Orofacial Pain – 112

6.6 Epidemiology of Dental Pain – 115

6.7 Conclusion – 118

References – 118

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_6

Learning Objectives

- To define pain and orofacial pain
- To describe the classification systems of orofacial pain
- To discuss the orofacial pain measures applied to oral epidemiology
- Evaluate the literature concerning the epidemiology of orofacial pain and dental pain

Final Considerations

Orofacial pain represents relatively common condition among people from different age groups that may impact on their daily routine. Dental pain resulting from dental caries is the predominant type of orofacial pain affecting mainly children, while orofacial pain among adults and elderly people is mainly referred as a chronic condition related to temporomandibular disorders and non-migrainous headaches. The diagnosis and management of chronic orofacial pain in clinical setting is complex requiring multiprofessional approach. The assessment of orofacial pain in research is also challenging, as there is no consensus with regard to the classification method of orofacial pain. Nonetheless, different unidimensional and multidimensional pain scales have been developed and used in epidemiologic studies, which may explain the important variation of orofacial pain estimates in population-based studies. Although demographics, individual characteristics (e.g. psychological factors) and socioeconomic status have been associated with orofacial pain, further evidence is needed to support population strategies to reduce orofacial pain.

6.1 Introduction

Orofacial pain is considered a major concern from subjects and healthcare professionals across different specialities including dentistry, medicine and public health. Overall, orofacial pain can be considered an umbrella term that covers a range of acute and chronic painful conditions involving the surrounding structures of the mouth, face and head [1]. Orofacial pain can be divided into *oral pain*, which refers to pain within the mouth and facial pain that includes pain originated below the orbitomeatal line and above the neck and anterior to the ears [2]. Orofacial pain encompasses a heterogeneous set of conditions including *toothache*, temporomandibular disorders, headache and sinusitis among others, which have different aetiological and risk factors. Therefore, orofacial pain may present as both chronic and acute conditions. *Dental pain* or toothache is the most common type of acute orofacial pain that predominantly occurs as a consequence of dental caries and has been receiving special attention from dental epidemiologists due to the meaningful prevalence in oral health surveys and greater occurrence among all types of orofacial pain [3–7].

There is a growing interest in assessing orofacial pain in clinical research as well as in large epidemiological studies. First, orofacial pain is a common condition despite the considerable variations of its occurrence across populations [8]. Second, orofacial pain represents a relevant burden in terms of health service utilisation [9]. Third, orofacial pain is a disabling condition associated with disability and functional impairments of daily routine, including on speaking, and chewing, that interferes on social engagement with family and friends, and emotional aspects of daily life [10]. Fourth, orofacial pain can negatively impact on *quality of life* and well-being. Persons experiencing orofacial pain had more absent days from work and school, greater sleep disturbance and eating difficulties [9, 11–13]. Finally, the management of orofacial pain requires a multidisciplinary and holistic team approach. The accurate and complete diagnosis is complex and frequently considered an 'understanding process' of pain genesis. In addition, therapeutic modalities for the management of orofacial pain require a patient-centred rather than a mouth-oriented approach and frequently combine pharmacologic, physical and psychologic therapies [1].

Orofacial pain is frequently associated with pathologic disorders related to somatic and neurologic structures in the head, face, neck and intraoral structures [14]. Dental pain (toothache) and *jaw pain* are the most common types of orofacial pain [15, 16]. The latter is musculoskeletal pain, located in the temporomandibular joints or in the masticatory muscles. *Temporomandibular disorders* and non-migrainous headaches (tension-type headaches) are by far the most common causes of the *chronic orofacial pain* conditions among adults and elderly people [17]. Nonetheless, herpes simplex and aphthous stomatitis are common oral lesions in adults that provoke acute pain. On the other hand, irreversible pulpitis (toothache) is likely the most common cause of acute orofacial pain in children. Other dental-related conditions related to orofacial pain include apical pain, pericoronitis, postendodontic surgery pain, exposed cementum or dentine, fractured tooth and alveolar osteitis [18].

Although the aetiology of most orofacial pain is still poorly understood, its occurrence at the population level is highly dependent on the rate of the different health conditions (e.g. dental caries) and the distribution of individual factors (e.g. age, gender, ethnicity) that generates pain. *Socioeconomic factors* (e.g. low income, social deprivation) and psychosocial factors (e.g. stress, anxiety) are considered the structural and intermediary determinants of health and inevitably influence orofacial pain prevalence [19].

The reported prevalence of orofacial pain varies considerably across studies. A previous systematic review reported the *prevalence of orofacial pain* as 13%, ranging from 1% (current check pain) to 48% (current oral or facial pain) [19]. The different definitions and measurements of orofacial pain (e.g. location of pain and pain scale) are considered the main aspects responsible for such large variation.

This chapter presents the definition and key concepts of pain and orofacial pain, main classification systems of orofacial pain, the different approaches to measure orofacial pain with special emphasis on instruments for surveys, epidemiological data concerning the prevalence and determinants of orofacial pain and dental pain.

6.2 Definition of Pain and Orofacial Pain

The long-established understanding of pain in medicine defines pain as a localised sensation of discomfort, distress or agony, occurring as a result of the stimulation of specialised nerve endings. *Pain* is considered a protective mechanism insofar against injuries as it persuades the affected person to remove or to withdraw from the source [20]. This definition is considered limited as it addresses one type of pain, the superficial pain somatic, as a consequence of noxious stimulation of cutaneous tissues by an external agent that affects the exteroceptive nociceptors. Since most pain occurs after the event or stimulus has taken place, pain is recognised as a sensation or an experience with a sensory dimension that includes the quality, intensity, location and duration of the initiating stimulus along with the cognitive, emotional and motivational dimensions [1]. Pain was also defined as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [21].

In a more recent and complete definition, unpleasant and emotional aspects of pain were incorporated in the concept. Therefore, pain is understood to represent not only a process induced solely by noxious stimulation but also a subjective psychologic state associated with one's experience of pain. Stedman's medical dictionary defines pain as an unpleasant sensation associated with actual or potential tissue damage and mediated by specific nerve fibres to the brain, where its conscious appreciation may be modified by various factors [22].

Orofacial pain is a broad term encompassing different groups of conditions including dental and oral pain, *temporomandibular pain*, neuropathic pain, *burning mouth*, chronic idiopathic facial pain and headaches. These conditions include pain within the trigeminal systems that are related to hard and soft tissues of the head, face, neck and intraoral structures [14, 18, 23]. *Temporomandibular disorders* comprise of three main groups. Of these, myofascial or arthromyalgic pain and dysfunctional joint pain (clicks, crepitus and/or locking) are the most common followed rarely by arthritis [24]. Dental pain, toothache or *odontogenic pain* refers to pain originating from the teeth or their supporting structures, the mucosa, gingivae, maxilla, mandible or periodontal membrane [18].

6.3 Diagnosis and Classification of Orofacial Pain

The establishment of the correct diagnosis in individuals with orofacial pain is a challenging process and notably troublesome. This is due to the complex relationship of somatic (Axis I) and psychosocial (Axis II) factors in the aetiology of chronic pain [14]. It should also be noted that several orofacial conditions share similar signs and symptoms, and the occurrence of multiple diagnoses is not an unusual situation. Although common and simple disorders are relatively easy to diagnose, it has been argued that a proper diagnosis and management of complex chronic orofacial conditions require an interdisciplinary approach involving different professionals [25]. The diagnosis of orofacial pain is also challenging due to complex histories, pathophysiology and associated psychosocial co-morbidities such as depression and anxiety [26].

Overall, there are three key elements in order to obtain the diagnosis of orofacial pain, including gathering information concerning the history of the pain, clinical examination and diagnostic tests (e.g. imaging tests). However, the initial diagnosis should be revised when the condition worsens or signs and symptoms remain after treatment, which suggests the individual failed to respond to the treatment [27].

The most popular classifications of orofacial pain include the International Headache Society criteria (IHS) and the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). Overall, the classifications for orofacial pain are usually based on the affected anatomical structures, person's reported symptoms and on the distinct approaches available on the management of orofacial pain. The use of a classification of orofacial pain may have different purposes. First, it assists the practitioner in the diagnosis. Second, it provides elements for planning the treatment and management of orofacial pain. Third, it favours patient acceptance and cooperation of the different stages of management. Four, the use of a reliable classification system in population surveys is a valuable tool to estimate the prevalence of different types of orofacial pain. Finally, its application in epidemiologic studies allows the identification of orofacial pain predictors and determinants.

Different classification schemes for orofacial pain have been developed over time. However, despite the efforts to classify TMD patients with the Research Diagnostic Criteria for TMD, headache patients with the International Headache Society criteria and orofacial pain with the American Academy of Orofacial Pain standards, clinical research indicates that each of these three methods is incomplete for a comprehensive diagnosis of orofacial pain patients [8]. The lack of validated diagnostic criteria is considered the major barrier for improved patient care and translational research [28]. There is no consensus concerning a unique and acceptable classification once all proposed classifications have pros and cons. Understanding the purpose of using the classification of orofacial pain (e.g. research, clinical practice) and the appropriate knowledge regarding the advantages and limitations of the classifications will allow the selection of one that is more adequate for its purpose (Table 6.1).

Table 6.1 Classification systems for orofacial pain

Classification	Organisation and author	Main characteristics
Research Diagnostic Criteria for Temporomandibular Disorders (RDC-TMD)	Dworkin or LeResche 1992 [29]	Based on the biopsychosocial model of pain and grouped in two axes. Axis I refers to physical diagnosis through examination protocol for the most common pain and nonpain-related TMDs. Axis II enables identification of relevant psychosocial characteristics of the patients
Diagnostic Criteria for Temporomandibular Disorders (DC-TMD)	Schiffman et al. 2014 [30]	Similar to RDC-TMD. Axis I was reorganised in pain-related TMDs and intra-articular TMDs. Axis II assesses the psychosocial and behavioural factors that impact on the patients' pain.
IASP Classification System	International Association for the Study of Pain (IASP) [31]	Pain syndromes grouped into nine major categories and then classified as generalised or localised. Orofacial pain disorders are placed under the category 'Relatively localised syndromes of the head and neck'
AACP classification of orofacial pain	American Academy of Craniofacial Pain (AACP) [32]	Follows IASP classification for neuralgias of the head and neck and the International Headache Society for headache disorders. TMDs are classified according to the masticatory muscle and joint disorders [33]
International Classification of Headache Disorders	International Headache Society (IHS) [34]	Classification for headache-related disorders, painful craniofacial neuropathies and other facial pains grouped in three parts. Part I and Part II are devoted to primary and secondary headaches. Part III refers to painful cranial neuropathies, other facial pains and headaches
Orofacial pain: guidelines for assessment, diagnosis and management	American Academy of Orofacial Pain (AAOP) [35]	Provides an informal classification scheme according different categories of craniofacial pain phenotypes based on a topographical approach and various tissue, structures or organ systems
Classification of chronic idiopathic orofacial pain	Woda et al. 2005 [36]	The classification system results from a 111-item self-reported questionnaire including questions on pain evaluation, impact of pain on health-related quality of life and psychological self-evaluation.
Classification of TMJ disorders	Stegenga 2010 [37]	Three main categories of temporomandibular joint (TMJ) disorders: arthritic disorders, growth disorders and nonarthritic disorders (noninflammatory)
Classification profile of TMD patients	Machado et al. 2012 [38]	Four groups based on clinical presentation and symptomatic profiles: acute muscle pain, nonpainful articular impairment, acute articular pain and chronic facial pain
Classification of orofacial pains	Okeson 2014 [39]	Pain classification based on symptomatology where pain conditions are grouped into superficial and deep somatic (response to the stimulation of normal neural receptors) and neurogenous (pains originate due to dysfunctional neurologic structures)

6.4 Measures and Instruments of Orofacial Pain

The *assessment of pain* is challenging due to subjective nature of the construct. Screening evaluation of orofacial pain and temporomandibular disorders (TMD) is recommended in clinical settings and should include a screening questionnaire, comprehensive history and physical examination [14]. However, these procedures are usually unfeasible in clinical and epidemiologic research, and the use of questionnaires to assess pain is widely acceptable.

There are multiple dimensions of pain that can be assessed, including (i) sensory (e.g. intensity, duration, location and frequency), (ii) affective/cognitive pain (e.g. pain unpleasantness) and (iii) impact of pain in daily life (e.g. physical, social, emotional and role functioning). While the importance of these domains is unquestionable, the measurement of the intensity of pain is the most commonly used parameter in clinical and research practices [40, 41].

Different instruments of pain assessment have been developed for different purposes, including the individual assessment of pain occurrence and intensity for clinical management as well as the evaluation of pain for clinical and epidemiologic research. Also, the use of such questionnaires has been incorporated into healthcare routines.

Overall, *pain scales* can be classified as unidimensional or multidimensional. The former instruments assess only one characteristic, usually presence of pain or pain intensity, while the latter ones assess different dimensions of pain. The unidimensional instruments are easier and faster to respond, and the cost is usually low, while multidimensional instruments assess the complexity of pain, which involves its intensity, location and affective and sensory qualities [42]. Although researcher's preferences influence the adoption of the pain scale, specific criteria should be considered when selecting the instrument. The scale should have good sensitivity as defined by the number of response categories provided in order to discriminate individuals with different levels of pain and its ability to detect treatment effects; the ease of administration and scoring; rates of correct responding; and the magnitude of the relationship between the scale and a 'best possible' combined measure of subjective pain intensity [40]. Likert-type and rating intensity pain scales should also be judged in terms of balance, which refers to the similar distance between each response option.

The assessment of pain in clinical research usually requires complex and multidimensional questionnaires to monitor pain over time as well as to investigate the effectiveness of therapeutic procedures. The McGill Pain Questionnaire is composed of three sections to assess the description of pain (What does your pain feel like?), pattern of pain (How does your pain changes over time?) and pain intensity (How strong is your pain?) [43]. The Brief Pain Inventory – Short Form (BPI) is a questionnaire that assesses multiple dimensions of patient's pain in the last 24 hours using a 10-point scale, including pain intensity and interference of pain with the patient's walking ability, daily activities, normal work, social activities, mood and sleep. The individual assesses his/her pain at its worst, at its least, on the average and right at the time of form completion [44].

The subjective intensity of pain is often measured using unidimensional instruments that are vastly employed in epidemiologic studies and health surveys due to feasibility and logistic reasons. There are several unidimensional pain instruments, including the visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS), behavioural rating scale (BRS) and faces rating scale (FRS) [45]. The prevalence of pain can also be assessed using a single-item questionnaire concerning whether the respondents have ever had pain.

These scales can refer to current pain or previous pain experience (e.g. pain during the past 30 days, pain during the past 3 months or pain during the past 6 months). The choice of measuring current or previous pain experience in research is related to the study's aims. However, although orofacial pain is a unique experience, clinicians and researchers must be cautious about recall bias when inquiring about previous pain experience, mainly when the studied population involves children and elderly people. Another approach is to use an open question asking the respondent to inform how long he or she has been experiencing pain.

The visual analogue scale (VAS) consists of a 10 cm line anchored by 2 extremes of pain: 'no pain' and 'unbearable pain'. Respondents are asked to mark on the continuous line, which represents their level of perceived pain intensity. The scale is scored by measuring the distance from the 'no pain' end to the patient's mark [40]. In the generic numerical rating scales (NRS), individuals are asked to circle one of the numeric options from 0 ('no pain') to 10 ('worst possible pain') that best describe the pain [40]. Therefore, NRS allows only a less-subtle distinction of pain levels compared to VAS, where the latter are theoretically unlimited number of possible answers. Other numerical scales are the 101-point numerical rating scale (NRS-101) and the 11-point Box Scale (BS-11). The NRS-101 consists of using a numerical scale from 0 to 100, with the 0 representing 'no pain' and the 100 representing 'pain as bad as it could be' [40]. The number stated by respondent is then used to rate his/her perceived level of pain intensity. The BS-11 consists of 11 numbers (0–10) surrounded by boxes where 0 represents one extreme of pain ('no pain') and 10 represents the opposite extreme ('pain as bad as it could be') [40].

The respondent is asked to place 'X' through the number representing his or her pain level [46].

The behavioural rating scale (BRS) such as the 6-point behavioural rating scale (BRS-6) assesses the intensity of pain according to its behavioural effects [40]. Each item on the BRS is given a score from 0 (least intense descriptor meaning 'no pain') to 5 (incapacitating pain). The intermediate intensity scores refer to different adjectives associated with pain. The respondent's intensity score is the number associated with the word he or she chooses as most descriptive of his or her pain level.

Verbal rating scale (VRS), also called nominal scale, adopts adjectives to describe different levels of pain. The respondent is asked to indicate the adjective that fits best to the pain intensity and because of that the verbal rating scales are easily to understand through assessing pain intensity using a qualitative approach. Similarly to VAS and NRS, VRS is anchored at two end points: 'no pain at all' and 'extremely intense pain'. Some VRs are the 4-point verbal rating scale (VRS-4) and the 5-point verbal rating scale (VRS-5) [40]. The former is frequently used in scale comparison studies, while the latter is a part of the McGill Pain Questionnaire [43], and it is commonly used in treatment outcome studies.

The face rating scales (FRSs) were developed to assess children's pain since FRSs facilitate reporting pain using a self-assessment scale [47–50]. Thus, it is essential that the child can understand the instructions and select a face that illustrates the pain he or she is experiencing. It is also suitable for adults and elderly people who experience difficulty using the numbers on the numerical rating scales or the words and adjectives on the behavioural and verbal rating scales. The International Association for the Study of Pain proposed The Faces Pain Scale – Revised (FPS-R) [31]. Another FRS is the Wong-Baker Faces Scale [49]. The FRS consists of six facial expressions suggesting various pain intensities. The respondent is asked to point the face that best describes how he or she feels. The far left face indicates 'no pain' or 'no hurt,' and the far right face indicates 'worst pain' or 'hurt worst'. In both scales, the 6 facial expressions correspond to the scores 0, 2, 4, 6, 8 or 10, counting from left to right, So '0' = 'no pain' and '10' = 'very much pain'. The FRS scale is intended to measure how children feel inside, not how their face looks. The Faces Pain Scale (FPS) is a 7-point scale composed of seven illustrations of faces. The FPS shows various degrees of pain that ranges from '0' (no pain) to '6' (most pain possible), representing increased pain order or intensity [47].

6.5 Epidemiology of Orofacial Pain

Academic research has made substantial progress in understanding the occurrence and distribution of orofacial pain. The scientific literature concerning the *epidemiology of orofacial pain* is large since it involves various disciplines in which pain is studied. Published papers in orofacial pain are distributed across more than 280 journals involving authors from nearly 55 countries [51]. However, nearly 90% of studies are published in dental journals [19]. Publications in the field of orofacial pain demonstrate a steady increase over the last decades [28]. The most common type o orofacial pain is dental pain [14]. The studies in orofacial pain epidemiology show a clear distinction concerning the location and/or origin of orofacial pain. Therefore, in this chapter, the epidemiologic studies in this field are didactically presented as orofacial pain (e.g. jaw joint pain, facial pain, burning mouth) and dental pain (e.g. toothache).

One of the main challenges to explore this literature is the different types of orofacial pain investigated, such as spontaneous self-reported pain, pain on mandibular movement and pain or tenderness on palpation. In addition, the studies in orofacial pain considered distinct aspects when defining 'case' of orofacial pain, including pain conditions associated with hard and soft tissues in the head, face, neck and intraoral structures [14]. Epidemiological studies on self-reported orofacial pain also adopted different recall periods, such as the following:

- Orofacial pain that had last a whole day or more or that had occurred several times in a year [52]
- Pain present for 1 day or longer in the past month and that such pain had been present for 3 months or longer [53]
- Pain that has lasted for 1 day or longer during the past month [54]
- Pain present for at least 3 months [55, 56]
- Pain in the last 7 days [57]
- Pain in the last month [11, 58–60]
- Pain in the last month that interfered with usual activities [12]
- Pain between 1 and 6 months [57]
- Pain over 6 months [57]
- Pain during the last 3 months [9, 17, 57, 60]
- Pain during the last 6 months [10, 61–65]
- Pain during the last 12 months [60, 66, 67]
- Pain at any time [67]

A systematic review grouped studies in orofacial pain as self-reported orofacial pain, self-reported *temporomandibular joint (TMJ) pain*, self-reported pain in the ear area, self-reported tongue or mouth pain, self-reported pain on chewing, pain on opening the mouth, pain on movement, TMJ joint and tenderness on palpation and other orofacial pain. The latter included pain reaction (pain on palpation or mandibular movement) and dull aching pain in a specific area from one or more trigger points in the affected muscle [19]. The aforementioned specific features of orofacial pain suggest important

methodological discrepancies between previous studies, which in turn explain the variations in the research findings [19]. Differences between studies regarding settings, data collection procedures and participant's characteristics are also responsible for variations on their results [19].

There is considerable variation in the prevalence of orofacial pain across epidemiological studies. Some studies suggest that orofacial pain prevalence may vary between 1% and 48% [19]. Another paper also reported a large variation of orofacial pain occurrence, ranging from 17% to 26% [8]. This large heterogeneity is possibly related to the diagnostic criteria or assessment tool of orofacial pain, as well as the location of the orofacial pain. The main characteristics of epidemiological studies in orofacial pain are presented in Table 6.2. The

Table 6.2 Individual characteristics of epidemiological studies on orofacial pain

Country	Study design	Sample size and age group	Prevalence orofacial pain
United States [52]	Cross-sectional	1016 adults aged 18 years and older from postal survey	12% (facial pain) 22% (head pain)
Sweden [58]	Cross-sectional	1009 adults aged 18–84 years from postal survey	8.9% (head, face, mouth)
United States [62]	Cross-sectional	45,711 participants from households	22% (any type)
United States [67]	Cross-sectional	1636 elderly people 65 years and older from households	7.7% (jaw joint pain), 6.9% (face pain), 6.4% (oral sores), 1.7% (burning mouth)
United States [63]	Longitudinal (4 years)	724 adults 45 years old and older from a vulnerable population	8.3% (jaw joint pain), 3.1% (face pain), 15.6% (painful oral sore), 1.6% (burning mouth)
England [11, 59, 60]	Cross-sectional	2504 patients aged 18–65 years registered in a general medical practice	23% orofacial pain only 26% (any type)
United States [64]	42 month follow-up	744 adults aged 45 years old and older from households and through telephone interview	9.2% (pain when chewing) 15.6% painful oral sores 36.7% orofacial pain in multiple sites
Korea [10]	Cross-sectional	1032 elders aged 55 years and older through telephone interview	15.5% (joint pain), 9.3% (face pain), 26.8% (toothache), 26.2% (oral sores), 14.2% (burning mouth)
England [54]	4 years follow-up	1680 patients aged 18–65 years from general medical practice	19% (face, mouth or jaws)
England [9]	Cross-sectional	2299 adults aged 18–75 years from general medical practice	7% (Chronic orofacial pain)
Sweden [60]	10 years longitudinal	9232 50-year-old subjects from 2 counties	4.7% (burning mouth) 12.7% (toothache)
England [53]	Cross-sectional	1735 adults 18–75 years from a general practice	7% (chronic orofacial pain)
Brazil [65]	Cross-sectional	267 workers from textile industries	32.2% (orofacial pain)
Portugal [55]	Cross-sectional	5094 adults aged 18 years and older from telephone interviews	12% (chronic head pain)
Canada [68]	Cross-sectional	5284 residents aged 7–79 years old from national survey	11.7% (pain in the mouth)
United States [17]	3 years longitudinal	2737 adults aged 18–44 years from communities	97.3% (any headache or facial pain)
United States [70]	Cross-sectional	89,976 children and adults from household survey	34.7% (headache/migraine) 49.2% (neck) 51.5% (face)

(continued)

Table 6.2 (continued)

Country	Study design	Sample size and age group	Prevalence orofacial pain
United Kingdom [12]	Cross-sectional	500,000 adults 40–69 years old registered with general medical practitioner	1.9% (facial pain) 0.88% (chronic facial pain)
India [56]	Cross-sectional	30–65 years old patients with orofacial pain symptoms from outpatient dental clinic	57.6% (toothache), 14.8 (TMJ pain), 13.2 (facial pain), 8% (oral sores), 6.4% (burning mouth)
Brazil [66]	Cross-sectional	890 adults and elders (18 years old and older) from households	55.5%
United States [72]	Cross-sectional	1668 patients aged 18–93 years from dental practices	16.1%
Netherlands [71]	Cross-sectional	1815 adults aged 18 years and older from two surveys	7.2% and 8.0% (TMD-pain)
Germany [57]	Cross-sectional	5039 people aged 14 years and older from two national surveys	4% (jaw pain – last 7 days) 0.9% (jaw pain – last 3 months)
Ecuador [69]	Cross-sectional	1407 children 6 months to 6 years old from community	33.8% (mouth pain)

participants were recruited from different settings, including general population [10, 17, 55, 57, 58, 61, 62, 66–68, 70, 71], vulnerable population [63], industries [65], health maintenance organisation [52], medical practices [9, 11, 12, 53, 54, 59, 60] and dental services [56, 72]. Information on orofacial pain as well as on demographic, socioeconomic characteristics was obtained using different methods such as individual interviews or self-completed questionnaires [12, 17, 56, 57, 62, 65, 66, 68–70, 72], postal surveys [9, 11, 52–54, 58–61], telephone interviews [10, 55, 67] or a combination of different methods [63, 64, 71].

The initial studies on the prevalence of orofacial pain probably occurred in the United States and Sweden. A previous systematic review identified 46 papers reporting cross-sectional data on orofacial pain. Most of the epidemiological data on orofacial pain was obtained from European and North American countries. They were conducted in Scandinavia, with 35% in Sweden, followed by Canada (16%), Finland (16%) and the United States (11%) [19]. A postal survey in Sweden involving 1009 adults and elderly people detected a prevalence of 14.6% of pain in head, face or mouth. In this sample, present pain of more than 6 months duration was reported far more often than short-lasting problems [58]. Two initial studies in the United States reported similar findings. A comprehensive household survey indicated that nearly 22% of the population experienced at least one type of orofacial pain during the last 6 months. In addition, having toothache and temporomandibular joint pain was reported by 12.2% and 5.3% of the adults. Approximately 11% of the participants complained about orofacial pain over a 6-month period [62]. American adults enrolled in a health maintenance organisation in Seattle (US) reported 26% and 12% of pain in the face and head, respectively [52].

The largest population data about orofacial pain were obtained in the United States [62] and in the United Kingdom [12]. The survey in the United States was conducted in the 1990s and involved 45,711 households. They reported the prevalence of toothache (12%), oral sores (8%), jaw joint pain (5%), face/check pain (1%) and burning mouth (1%). More recently, cross-sectional population data on facial pain from the UK Biobank study was analysed. The study suggested that facial prevalence was lower than reported in previous population surveys, as the overall prevalence of facial pain was nearly 2.0%. Another interesting finding was the similar prevalence between acute and chronic facial pain [12]. The imprecision when estimating the prevalence of orofacial pain has been highlighted by a systematic review that suggested the need to recruit adequate sample sizes in future studies [19].

Information regarding temporal trends in orofacial pain obtained from longitudinal studies is scarce. Reported orofacial symptoms over the course of a 10-year period (1992–2002) were investigated in 50-year-old residents in two Swedish counties [61]. There was an increase in toothache in the last year from 12.7% to 16.4%, and tooth sensitivity prevalence rose from 34.9% to 57.6%. The occurrence of other intraoral symptoms was relatively stable between the investigated periods [61]. The variation of temporomandibular disorders

within 5 years period involving 2737 community-based American adults was assessed. History of orofacial pain at baseline was reported by 15% of the participants of the OPPERA prospective cohort study. The incidence per annum of orofacial pain (median = 2.8 years per person) was 3.5%, and painful jaw symptoms were described most frequently in terms of an ache, soreness or tenderness [17].

The aetiology of the different types of orofacial pain varies depending on the nature and the location of the pain. Acute forms of orofacial pain are most commonly related to tooth or periodontal diseases. Toothache as a result of dental caries is the essential factor for dental pain occurrence. However, the aetiology of chronic orofacial pain is still poorly understood. Chronic orofacial pain is often diagnosed as conditions such as temporomandibular disorders and atypical facial pain [73]. The identification of an unambiguous cause of chronic orofacial pain is complex since the dynamic equilibrium between the components of the masticatory system acknowledges the importance of loss of structural integrity, altered function, biomechanical strains and stresses in the system that can compromise the adaptability and then results in a dysfunction or pathology [1].

Age and gender are probably the most factors investigated in studies involving orofacial pain [9, 10, 13, 17, 19, 52, 56, 60, 61, 64, 71, 72]. Overall, the studies did not show any particular pattern of orofacial pain with regard to age. Some studies suggest orofacial pain is more prevalent among younger adults than older ones [13, 52, 60, 71]. On the other hand, other research showed the increase of orofacial prevalence with greater age [9, 11, 17, 64]. A population-based survey in Korea involving residents aged 55 years or over revealed a positive correlation between toothache and greater age. However age was not associated with other forms of orofacial pain, such as joint pain, face pain, oral sores and burning mouth [10]. Age was not related to orofacial pain in large surveys involving adults and elderly people in the United States [72] as well as with adults in Sweden [74]. In general, the prevalence of orofacial pain was higher in women than in men [9, 10, 13, 60, 62, 71, 72]. Nonetheless, some studies did not find gender differences of orofacial pain prevalence [17, 56, 68]. Although the prevalence of orofacial symptoms was similar between males and females adults in India, the intensity of pain was greater among the latter group [56].

Other potential predictors of orofacial pain include socioeconomic status, local mechanical factors, *psychological factors* and co-morbidities [9, 11, 12, 15, 17, 19, 52, 54, 59–61, 64, 68]. In Sweden, the increase in orofacial pain over 10 years was accompanied by differences in demographic, occupational, general and oral health conditions [61]. Evidence suggests that orofacial pain was associated with poor socioeconomic background and social deprivation [11, 12, 15, 68]. People living in the most deprived areas in South-East Cheshire in England were more likely to report orofacial pain than those from the most affluent ones [11]. The UK Biobank study concluded that facial pain was associated with various measures of social and economic status. The greater prevalence of facial pain was linked to low income, unemployment, poor education level and area-level deprivation [12]. Oral pain was more common in the lowest-income groups in Canada [68]. However, some studies did not find association of income and education with different types of orofacial pain [10, 17, 71].

The possible role of psychosocial factors on orofacial pain has been investigated (e.g. depression, anxiety, stress) [9, 11, 12, 52, 75]. A 2-year follow-up study in England concluded that health anxiety is a predictor of onset of chronic orofacial pain [11]. Similarly, experiencing life events, depression and anxiety increased the prevalence of chronic orofacial pain [9]. Somatisation and family stress were also associated with face pain in the United States [52].

6.6 Epidemiology of Dental Pain

Evidence suggests a large variation on the *prevalence of dental pain* in previous studies conducted in different countries and age groups. The prevalence of dental pain while biting or chewing in the last 6 months was 7% among Americans aged 65 years and over [15]. Dental pain in the lifetime was reported by only 9.1% of patients aged 18–93 years from a dental practice-based research network in the United States [72]. On the other hand, a population-based survey conducted among Iranian adults over 18 years old found a prevalence of dental pain in the last 6 months of 55.1% [76].

Differences in the age group of the study, the recall period of the dental pain and characteristics of the population (e.g. country, level of deprivation) are the possible reasons for such discrepancies. For instance, dental pain in the lifetime was reported by 74% of adults from a specific vulnerable group in the United States. In this study, only those who had experienced a toothache during the previous 12 months were included, which may explain the high prevalence of lifetime dental pain [77]. It is interestingly to note that despite important differences, some studies reported similar rates of dental pain. The prevalence of dental pain among residents of all ages from a socially deprived rural area in India was 28% [78]. This was similar to the prevalence among Korean older adults aged 55 years and over (27%) [10] and adult workers from textile industries in the South of Brazil (26%) [65].

The assessment of self-reported dental pain has been investigated in national oral health surveys in the United Kingdom [5], United States [15] and Brazil [79–81]. Nonetheless, primary studies in dental pain were mainly conducted in the latter country [3, 4, 6, 7, 65, 82–85, 86–89] (Table 6.3).

Similar to studies in orofacial pain, dental pain has been investigated considering different recall periods of

Table 6.3 Individual characteristics of epidemiological studies on dental pain

Country, year	Studied sample and setting	Recall period	Prevalence
United States [67]	1636 elderly people 65 years and older	Last 12 months	12%
United States [63]	724 adults 45 years old and older from a vulnerable population	Last 6 months	12%
United States [15]	33,073 adults aged 20 years over from the 1989 National Health Interview Survey (NHIS)	While biting or chewing in the last 6 months	14.5% (20–64 years old) 7.0% (65 years and older)
United States [64]	42 month follow-up 744 adults aged 45 years and older	Last 6 months	12%
Korea [10]	1032 elders aged 55 years and older over through telephone interview	Lifetime dental pain	26.8%
Brazil [3]	169 12- and 13-year-old schoolchildren enrolled in a public school	Last 12 months	33.7%
Brazil [4]	414 18-year-old males from the army conscription	Lifetime dental pain	21.2%
Brazil [82]	1052 14–15 years-old schoolchildren	Last 6 months	33.6% dental pain in the
United Kingdom [5]	4942 adults aged 16 years and over from the UK Adult Dental Health Survey	Last 12 months	28%
Brazil [83]	3353 adults aged 20 years and older from a population-based survey	Lifetime dental pain	17.7%
Brazil [84]	601 8- and 9-year-old schoolchildren	Lifetime dental pain last month	45.9% 15.6%
US [77]	903 adults aged 21 years and older from a vulnerable population	Last 12 months	44.1%
Tanzania [90]	1745 students aged 10–19 years in a deprived district	Unclear	30.2%
Brazil [85]	2022 adults aged 20–59 years from a population-based study	Last 6 months	18.0%
Brazil [86]	4249 12-year-old and 1566 15-year-old schoolchildren	Last 6 months	25.6%
Brazil [65]	267 workers from textile industries	Lifetime dental pain	25.5%
Brazil [6]	1129 children aged 5 years from a population-based birth cohort	Lifetime dental pain	16.5%
Brazil [87]	744 adults aged 35–44 years from a population-based survey	Last 6 months	24.3%
Brazil [79]	9779 adults aged 35–44 years from the national oral health survey	Last 6 months	21%
Iran [76]	1800 adults from a population-based survey	Last 6 months	55.1%
Brazil [88]	661 15–74 years from a population-based survey	Last 6 months	26.8%
Brazil [89]	843 preschool children	Lifetime dental pain	9.4%

Table 6.3 (continued)

Country, year	Studied sample and setting	Recall period	Prevalence
United States [72]	1668 patients aged 18–93 years from dental practices	Lifetime dental pain	9.1%
India [78]	630 low socioeconomic status residents (mean age = 32.8 ± 16.7 years) in a rural area	Last 6 months	28.3%
Mexico [91]	1404 schoolchildren aged 6–12 years	Last 12 months	49.9%
Australia [92]	9875 schoolchildren aged 4–17 years from a 14-year prospective study	Lifetime dental pain	22.8%
Brazil [7]	1233 12-year-old schoolchildren	Last 6 months	16.7%
Brazil [80, 81]	7280 5-year old from the national oral health survey	Last 6 months	22%
United States [93]	1114 US veterans	Last moth	25.1%

pain assessment, including dental pain in the last month [93], dental pain in the last 6 months [7, 63, 64, 76, 78–82, 85, 86–88], dental pain in the last 12 months [3, 5, 67, 91] and dental pain one in life (lifetime dental pain) [4, 6, 10, 65, 72, 83, 89, 92]. Some studies used more than one recall period [77, 84]. One study assessed dental pain in the last 6 months while biting [15].

Dental pain is highly prevalent in children [6, 7], even in contemporary populations characterised by low levels of caries [94]. Dental pain is consistently associated with untreated dental caries and dental caries experience at population level in children and adolescents. The above-mentioned association seems to be more pronounced among those from low socioeconomic status [3, 6, 7, 94]. Dental caries measures, including untreated cavities and dental caries experience, are also the main factors related to dental pain in younger adults and adults [4, 88].

Demographic characteristics have been associated with dental pain. Younger adults [83, 85, 86] and female participants [83, 85, 92] reported more dental pain than their counterparts. In Iran, individuals between the ages of 26 and 65 were more likely to have a history of dental pain than those 25 years or less [76]. A systematic review on children and adolescents suggested that lifetime prevalence of dental pain was greater among older children [94].

Dental pain prevalence was higher among non-whites children [7], indigenous children [80], dark-skinned children [6, 86] and black people [83, 85] than white participants. Dental pain was more likely to be reported by non-Hispanic blacks than non-Hispanic whites or Hispanics among elderly people aged 65 years and older [15].

Behaviours such as smoking, alcohol problems and poor diet (e.g. low-fruit intake, high-fried food) were associated with dental pain [85, 91]. Regular tooth brushing had no significant effect on the prevalence of toothache in one study [76], but tooth brushing at least once a day was inversely associated with dental pain [91]. Use of dental services in the last year and regular use of dental services were protective factors for dental pain among adults [76, 85, 88]. Pattern of dental attendance was the main predictor of prevalence and severity of pain in Brazilian schoolchildren [82]. Few studies assess the relationship of psychosocial factors and dental pain. Adults with mental or psychological illness were more likely to have a history of dental pain [76].

The evidence that poor socioeconomic status is a predictor of greater occurrence of dental pain is considerable. In the United Kingdom, manual workers were 20% more likely to report dental pain in the last 12 months than non-manual workers after controlling for gender and age [5]. Living in poverty, defined by income below the threshold for specific family size and composition, was associated with dental pain in the last 6 months in American adults. In addition, those with poor socioeconomic status were more likely to endure their pain without the benefit of dental care, while the pain was present [94]. Adults with low per capita income living in the urban area of a medium-sized city in Southern Brazil reported more dental pain than those with higher income [85]. Similarly, younger adults with low family income were almost two times more likely to have dental pain than those with higher income [4]. Dental pain was also related to low educational attainment and low family income in adults [4, 76].

Children and adolescents from low socioeconomic groups report more dental pain than those from affluent groups [94]. Dental pain was more frequent in schoolchildren from households with low income than those

from high ones [3, 6, 7, 80, 86]. It was also observed that dental pain intensity and prevalence were higher among children whose parents had a lower educational level [3, 6, 7, 86]. Children from low social class and those living in poor housing conditions also reported more dental pain [82, 91]. A longitudinal study concluded that low family income among Australian schoolchildren aged 4–17 years was a significant predictor of dental pain after 14 years of follow-up [92].

Few studies assessed the relationship between contextual factors and dental pain [80, 86, 88, 90]. Dental pain was significantly more prevalent in urban areas than in rural areas in Tanzania [90]. Data from the Brazilian national oral health survey showed that the prevalence of dental pain among 5 years old children was higher among those living in cities with lower social development and with a higher percentage of their population with incomplete primary education [80]. Adolescents living in more developed areas of the city of Sao Paulo, Brazil, were 33% less likely to report dental pain than among those living in less developed areas [86]. In addition, individuals living in neighbourhoods with high levels of social capital were less likely to report dental pain than those living in neighbourhoods with low social capital [88].

6.7 Conclusion

- Orofacial pain is a relatively common condition that involves a group of acute and chronic conditions affecting the mouth, face and head.
- The aetiology of orofacial pain is complex, and it is strongly related to pathologic disorders of somatic and neurologic structures in the head, face, neck and intraoral structures.
- Dental pain and musculoskeletal jaw pain are the most common types of orofacial pain. The former is the most common type of acute orofacial pain that predominantly occurs as a consequence of dental caries.
- The prevalence of orofacial pain and dental pain varies significantly between studies. This is possibly explained by the differences in the methodological choices such as the location of orofacial pain investigated, the recall period of pain and demographic and socioeconomic characteristics of the studied samples.
- Future longitudinal epidemiological studies are necessary to enhance the understanding of the risk factors of orofacial pain and dental pain as well the role of orofacial pain on quality of life and well-being.

References

1. Okeson JP. The nature of pain. In: Bell's orofacial pains: the clinical management of orofacial pain. 6th ed. Carol Stream: Quintessence Publishing Company Inc; 2005. p. 3–12.
2. Zakrzewska JM, Hamlyn PJ. Facial pain. In: Crombie I, editor. Epidemiology of pain. Seattle: IASP Press; 1999. p. 171–202.
3. Nomura LH, Bastos JL, Peres MA. Dental pain prevalence and association with dental caries and socioeconomic status in schoolchildren, Southern Brazil, 2002. Braz Oral Res. 2004;18(2):134–40.
4. Bastos JL, Nomura LH, Peres MA. Dental pain, socioeconomic status, and dental caries in young male adults from southern Brazil. Cad Saude Publica. 2005;21(5):1416–23.
5. Pau A, Croucher RE, Marcenes W. Demographic and socioeconomic correlates of dental pain among adults in the United Kingdom, 1998. Br Dent J. 2007;202(9):E21.
6. Boeira GF, Correa MB, Peres MA, Peres KG, Santos IS, Matijasevich A, Barros AJD, Demarco FF. Caries is the main cause for dental pain in childhood: findings from a birth cohort. Caries Res. 2012;46:488–95.
7. Guskuma RC, Lages VA, Hafner MB, Rando-Meirelles MPM, Cypriano S, Sousa MDLR, Batista MJ. Factors associated with the prevalence and intensity of dental pain in children in the municipalities of the Campinas Region, São Paulo. Rev Paul Pediatr. 2017;35:322–30.
8. Benoliel R, Birman N, Eliav E, Sharav Y. The International Classification of Headache Disorders: accurate diagnosis of orofacial pain? Cephalalgia. 2008;28:752–62.
9. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? Int J Epidemiol. 2006;35:468–76.
10. Chung JW, Kim JH, Kim HD, et al. Chronic orofacial pain among Korean elders: prevalence, and impact using the graded chronic pain scale. Pain. 2004;112(1–2):164–70.
11. Aggarwal VR, Macfarlane TV, Macfarlane GJ. Why is pain more common amongst people living in areas of low socioeconomic status? A population-based cross-sectional study. Brit Dent J. 2003;194:383–7.
12. Macfarlane TV, Beasley M, Macfarlane GJ. Self-reported facial pain in UK biobank study: prevalence and associated factors. J Oral Maxillofac Res. 2014;5(3):e2.
13. Haviv Y, Zini A, Etzioni Y, Klitinich V, Dobriyan A, Sharav Y, Benoliel R, Almoznino G. The impact of chronic orofacial pain on daily life: the vulnerable patient and disruptive pain. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;123(1):58–66.
14. Okeson JO. Orofacial pain: guidelines for assessment, classification, and management. Chicago/London: Quintessence Publishing Company Inc; 1996.
15. Vargas CM, Macek MD, Marcus SE. Sociodemographic correlates of tooth pain among adults: United states, 1989. Pain. 2000;85(1–2):87–92.
16. Zakrzewska JM. Multi-dimensionality of chronic pain of the oral cavity and face. J Headache Pain. 2013;14:37.
17. Slade GD, Bair E, Greenspan JD, et al. Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study. J Pain. 2013;14(T20–32):e21–3.
18. Renton T. Dental (odontogenic) pain. Rev Pain. 2011;5:2–7.
19. Macfarlane TV, Glennu AM, Worthington HV. Systematic review of population-based epidemiological studies of oro-facial pain. J Dent. 2001;29:451–67.

20. Dorland WAN. Dorland's illustrated medical dictionary, vol. 11724. 27th ed. Philadelphia: Saunders; 1988.
21. IASP International Association for the Study of Pain. 1994. Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Defi.
22. Stedman TL. Stedman's medical dictionary, vol. 1297. 27th ed. Baltimore: Lippincott Williams & Wilkins; 2000.
23. Drangsholt M, Leresche L. Epidemiology of orofacial pain. In: Zakrzewska JM, editor. Orofacial pain. Oxford: Oxford University Press; 2009. 209 p.
24. Schiffman E, Ohrbach R. Executive summary of the diagnostic criteria for temporomandibular disorders for clinical and research applications. J Am Dent Assoc. 2016;147:438–45.
25. Raskin NH. Headache. 2nd ed. New York: Churchill Livingstone; 1988.
26. Ghurye S, Mcmillan R. Orofacial pain – an update on diagnosis and management. Br Dent J. 2017;223:639–47.
27. Zakrzewska JM, Okenson J. Classification and diagnosis of orofacial pain. In: Zakrzewska JM, editor. Orofacial pain. New York: Oxford University Press Inc; 2009. p. 43–52.
28. Hargreaves KM. Orofacial pain. Pain. 2011;152:S25–32.
29. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 1992;6:301–55.
30. Schiffman E, Ohrbach R, et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the international RDC/TMD consortium network* and orofacial pain special interest Groupdagger. J Oral Facial Pain Headache. 2014;28(1):6–27.
31. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994.
32. American Academy of Craniofacial Pain. Craniofacial pain: a handbook for assessment, diagnosis and management. Chattanooga: Chroma, Inc.; 2009.
33. Pertes RA, Gross SG. Clinical management of temporomandibular disorders and orofacial pain. Chicago: Quintessence Books; 1995.
34. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808.
35. De Leeuw R, Klasser GD. Orofacial pain: guidelines for assessment, diagnosis, and management. Chicago: Quintessence Publishing Company Inc; 2013.
36. Woda A, Tubert-Jeannin S, et al. Towards a new taxonomy of idiopathic orofacial pain. Pain. 2005;116:396–406.
37. Stegenga B. Nomenclature and classification of temporomandibular joint disorders. J Oral Rehabil. 2010;37:760–5.
38. Machado L, Nery MB, et al. Profiling the clinical presentation of diagnostic characteristics of a sample of symptomatic TMD patients. BMC Oral Health. 2012;12:26.
39. Okeson JP. Bell's oral and facial pain. Chicago: Quintessence Publishing Company Inc; 2014.
40. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27:117–26.
41. Hugueta A, Stinsonb JN, McGratha PJ. Measurement of self-reported pain intensity in children and adolescents. J Psychosom Res. 2010;68:329–36.
42. Martinez JE, Grassi DC, Marques LG. Analysis of the applicability of different pain questionnaires in three hospital settings: outpatient clinic, ward and emergency unit. Rev Bras Reumatol. 2011;51(4):299–308.
43. Melzack R. The McGill pain questionnaire: major properties and scoring methods. Pain. 1975;1:277–99.
44. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin brief pain questionnaire to assess pain in cancer and other diseases. Pain. 1983;17(2):197–210.
45. Haefeli M, Elfering A. Pain assessment. Eur Spine J. 2006;15:S17–24.
46. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis. 1978;37(4):378–81.
47. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The faces pain scale for the self-assessment of the severity of pain experienced by children: development, initial validation and preliminary investigation for ratio scale properties. Pain. 1990;41:139–50.
48. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The faces pain scale – revised: toward a common metric in pediatric pain measurement. Pain. 2001;93:173–83.
49. Wong-Baker FACES Foundation. Wong-Baker FACES® pain rating scale. 2018. Retrieved [Date] with permission from http://www.WongBakerFACES.org.
50. International Association for the Study of Pain. Faces pain scale – Revised, ©2001. www.iasp-pain.org/FPSR, https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1519&navItemNumber=577.
51. Robert C, Wilson CS, Donnadieu S, Gaudy JF, Arreto CD. Bibliometric analysis of the scientific literature on pain research: a 2006 study. Pain. 2008;138:250–4.
52. Von Korff M, Dworkin SF, LeResche L, Kruger A. An epidemiologic comparison of pain complaints. Pain. 1988;32:173–83.
53. Aggarwal VR, Macfarlane GJ, Farragher TM, McBeth J. Risk factors for onset of chronic oro-facial pain – results of the North Cheshire oro-facial pain prospective population study. Pain. 2010;149:354–9.
54. Macfarlane TV, Blinkhorn AS, Craven R, et al. Can one predict the likely specific orofacial pain syndrome from a self-completed questionnaire? Pain. 2004;111(3):270–7.
55. Azevedo LF, Costa-Pereira A, Mendonça L, Dias CC, Castro-Lopes JM. Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. J Pain. 2012;13(8):773–83.
56. Oberoi SS, Hiremath SS, Yashoda R, Marya C, Rekhi A. Prevalence of various orofacial pain symptoms and their overall impact on quality of life in a Tertiary Care Hospital in India. J Maxillofac Oral Surg. 2014;13(4):533–8.
57. Türp JC, Schmutzer G, Brähler E, Häuser W. Prevalence of self-reported jaw pain in Germany: two cross-sectional surveys of the general German population. Clin Oral Invest. 2016;20:1895–901.
58. Brattberg G, Thorslund M, Wikman A. The prevalence of pain in a general population. The results of a postal survey in a county of Sweden. Pain. 1989;37:215–22.
59. Macfarlane TV, Blinkhorn AS, Davies RM, Kincey J, Worthington HV. Oro-facial pain in the community: prevalence and associated impact. Community Dent Oral Epidemiol. 2002;30(1):52–60.
60. Macfarlane TV, Blinkhorn AS, Davies RM, Ryan P, Worthington HV, Macfarlane GJ. Orofacial pain: just another chronic pain? Results from a population-based survey. Pain. 2002;99:453–8.
61. Unell L, Johansson A, Carlsson GE, Halling A, Söderfeldt B. Changes in reported orofacial symptoms over a ten-year period as reflected in two cohorts of fifty-year-old subjects. Acta Odontol Scand. 2006;64:202–8.
62. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. JADA. 1993;124(10):115–21.

63. Riley JL, Gilbert GH. Orofacial pain symptoms: an interaction between age and sex. Pain. 2001;90(3):245–56.
64. Riley JL, Gilbert GH, Heft MW. Socioeconomic and demographic disparities in symptoms of orofacial pain. J Pub Health Dent. 2003;63:166–73.
65. Lacerda TL, Ribeiro JD, Ribeiro DM, Traebert J. Prevalence of orofacial pain and its impact on the oral health-related quality of life of textile industries workers of Laguna, SC, Brazil. Ciencia e Saude Coletiva. 2011;16:4275–82.
66. De Siqueira SR, Vilela TT, Florindo AA. Prevalence of headache and orofacial pain in adults and elders in a Brazilian community: an epidemiological study. Gerodontology. 2015;32(2):123–31.
67. Riley JL, Gilbert GH, Heft MW. Orofacial pain symptom prevalence: selective sex differences in the elderly? Pain. 1998;76:97–104.
68. Ravaghi V, Quiñonez C, Allison PJ. Oral pain and its covariates: findings of a Canadian population-based study. J Can Dent Assoc. 2013;79:d3.
69. So M, Ellenikiotia YA, Husby HM, Paz CL, Seymour B, Sokal-Gutierrez K. Early childhood dental caries, mouth pain, and malnutrition in the Ecuadorian Amazon region. Int J Environ Res Public Health. 2017;14:550.
70. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of persistent pain in the U.S. adult population: new data from the 2010 National Health Interview Survey. J Pain. 2014;15(10):979–84.
71. Visscher CM, Ligthart L, Schuller AA, Lobbezoo F, de Jongh A, van Houtem CM, Boomsma DI. Comorbid disorders and sociodemographic variables in temporomandibular pain in the general Dutch population. J Oral Facial Pain Headache. 2015;29:51–9.
72. Horst OV, Cunha-Cruz J, Zhou L, Manning W, Mancl L, DeRouen TA. Prevalence of pain in the orofacial regions in patients visiting general dentists in the Northwest Practice-based Research Collaborative in Evidence Based Dentistry research network. J Am Dent Assoc. 2015;146(10):721–8.e3.
73. Leden I, Rosenberg C. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain. 1993;9(3):174-82
74. LeResche L. Epidemiology of orofacial pain. In: Lund JP, Lavigne GJ, Dubner R, Sessle BJ, editors. Orofacial pain: from basic science to clinical management. Chicago: Quintessence Publishing Company Inc; 2001.
75. Hanindriyo L, Yoshihara A, Takiguchi T, Miyazaki H. Chronic intra oral pain and depressive symptoms in Japanese community-dwelling elderly: a longitudinal study. Community Dent Health. 2018;35(2):102–8.
76. Kakoei S, Parirokh M, Nakhaee N, Jamshidshirazi F, Rad M, Kakooei S. Prevalence of toothache and associated factors: a population-based study in Southeast Iran. Iran Endod J. 2013;8(3):123–8.
77. Cohen LA, Bonito AJ, Akin DR, Manski RJ, Macek MD, Edwards RR, Cornelius LJ. Toothache pain: Behavioral impact and self-care strategies. Spec Care Dentist. 2009;29(2):85-95. doi: 10.1111/j.1754-4505.2008.00068.x.
78. Jaiswal AK, Pachava S, Sanikommu S, Rawlani SS, Pydi S, Ghanta B. Dental pain and self-care: a cross-sectional study of people with low socio-economic status residing in rural India. Int Dent J. 2015;65(5):256-60. doi: 10.1111/idj.12180.
79. Hafner MB, Zanatta J, Rasera Zotelli VL, Batista MJ, Sousa Mda L. Perception of toothache in adults from state capitals and interior cities within the Brazilian geographic regions. BMC Oral Health. 2013;13:35. doi: 10.1186/1472-6831-13-35.
80. Ferreira-Júnior OM, Freire MCM, Moreira RS, Costa LR. Contextual and individual determinants of dental pain in preschool children. Community Dent Oral Epidemiol 2015;43: 349–356.
81. Freire MDCM, Corrêa-Faria P, Costa LR. Effect of dental pain and caries on the quality of life of Brazilian preschool children. Rev Saude Publica. 2018;52:30.
82. Goes PS, Watt R, Hardy RG, Sheiham A. The prevalence and severity of dental pain in 14–15 year old Brazilian schoolchildren. Community Dent Health. 2007;24:217–24.
83. Bastos JL, Peres MA, Peres KG, Araujo CLP, Menezes AMB. Toothache prevalence and associated factors: a life course study from birth to age 12 yr. Eur J Oral Sci. 2008;116:458–66.
84. Barrêto EPR, Ferreira EF, Pordeus IA. Determinant factors of toothache in 8- and 9-year-old schoolchildren, Belo Horizonte, MG, Brazil. Braz Oral Res. 2009;23:124–30.
85. uhnen M, Peres MA, Masiero AV, Peres KG. Toothache and associated factors in Brazilian adults: a cross-sectional population-based study. BMC Oral Health. 2009;9:7. doi: 10.1186/1472-6831-9-7.
86. Peres MA, Peres KG, Frias AC, Antunes JL. Contextual and individual assessment of dental pain period prevalence in adolescents: a multilevel approach. BMC Oral Health. 2010;13(10):20.
87. De Pinho AMS, Campos ACV, Ferreira EF, Vargas AMD. Toothaches in the daily lives of Brazilian adults. Int J Environ Res Public Health. 2012;9:2587–600.
88. Santiago BM, Valença AMG, Vettore MV. Social capital and dental pain in Brazilian northeast: a multilevel cross-sectional study. BMC Oral Health. 2013;13:2.
89. Clementino MA, Gomes MC, Pinto-Sarmento TC, Martins CC, Granville-Garcia AF, Paiva SM. Perceived Impact of Dental Pain on the Quality of Life of Preschool Children and Their Families. PLoS One. 2015 Jun 19;10(6):e0130602. doi: 10.1371/journal.pone.0130602. eCollection 2015.
90. Mashoto KO, Astrøm AN, David J, Masalu JR. Dental pain, oral impacts and perceived need for dental treatment in Tanzanian school students: a cross-sectional study. Health and Quality of Life Outcomes 2009, 7:73 doi:10.1186/1477-7525-7-73.
91. Escoffié-Ramirez M, Ávila-Burgos L, Baena-Santillan ES, Aguilar-Ayala F, Lara-Carrillo E, Minaya-Sánchez M, Mendoza-Rodríguez M, Márquez-Corona ML, Medina-Solís CE. Factors associated with dental pain in Mexican schoolchildren aged 6 to 12 years. Biomed Res Int. 2017;2017: 7431301.
92. Ghorbani Z, Peres MA, Liu P, Mejia GC, Armfield JM, Peres KG. Does early-life family income influence later dental pain experience? A prospective 14-year study. Aust Dent J. 2017;62:493–9.
93. Hicks TA, Wilson SM, Thomas SP, Dennis PA, Neal JM, Calhoun PS. Low income as a multiplicative risk factor for oral pain and dental problems among U.S. Veteran Smokers. Int J Behav Med. 2018;25:67–73.
94. Slade GD. Epidemiology of dental pain and dental caries among children and adolescents. Community Dent Health. 2001;18(4):219-27.

Dental Fluorosis: Epidemiological Aspects

Loc G. Do and Diep H. Ha

Contents

7.1 Introduction – 122
7.1.1 Aetiology and Clinical Appearance of Dental Fluorosis – 122
7.1.2 Historical Trend of Dental Fluorosis – 123
7.1.3 Risk Factors for Dental Fluorosis – 124
7.1.4 The Measurement of Dental Fluorosis – 126
7.1.5 Public Opinion on Fluorosis – 129

References – 130

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_7

Learning Objectives

- Understand aetiology and clinical appearance of dental fluorosis
- Understand historical trend of dental fluorosis
- Familiarise with main indices of dental fluorosis
- Understand impact of dental fluorosis

7.1 Introduction

The use of fluorides for oral health has always involved a balance between the protective benefit against dental caries and the risk of developing fluorosis. The association between fluoride and dental health was established as a result of determining the causes of dental fluorosis (enamel mottling). However, it was the benefit of the exposure to fluoride from between 0.7 and 1.2 ppm in public water supplies for the prevention of dental caries that soon became the dominant public health policy. It has been recognised that there is a level of exposure to fluoride that is associated with near-maximal reduction in caries experience with minimal risk of fluorosis (see Fig. 7.1). Establishing that level of exposure has always been a primary goal of population oral health research.

In the population, dental fluorosis serves as the "canary in the coal mine", alerting both members of the public and public health authorities to potential overexposure to sources of fluoride. With the onset of fluoridation and fast expansion of fluoridated toothpaste use in the 1960s and 1970s, the improvement in dental health that followed fluoridation blunted attention or interest in the low prevalence of fluorosis. However, as the prevalence of fluorosis increased during the 1980s, research began to focus on fluorosis again. Hence, it is important to understand epidemiological aspects of dental fluorosis.

7.1.1 Aetiology and Clinical Appearance of Dental Fluorosis

Dental fluorosis is a developmental defect in tooth enamel that is caused by excessive exposure to fluoride during the enamel formation period [1]. Dental fluorosis is the most common adverse effect of fluoride use in prevention of dental caries [2, 3]. Fluoride is considered a necessary factor in the aetiology of fluorosis. However, the presence of fluoride may have an effect only during the tooth development stage. Several authors considered a specific "window" period during enamel development as critical for fluorosis to occur [4, 5]. Other authors suggested that the duration of fluoride exposure during the amelogenesis, rather than specific risk periods, would have more impact on the aetiology of dental fluorosis [6, 7]. However, there was general agreement that exposure during the post-secretory or early maturation period of enamel development may pose a higher risk for fluorosis.

Fluorosed enamel is histologically characterised by hypocalcification and subsurface porosity [8, 9]. Clinically, fluorosis varies from barely visible white striations on the tooth surface to staining and pitting of enamel [1]. In the mild form, the structural arrangement of the crystals in the outer layer of enamel is microscop-

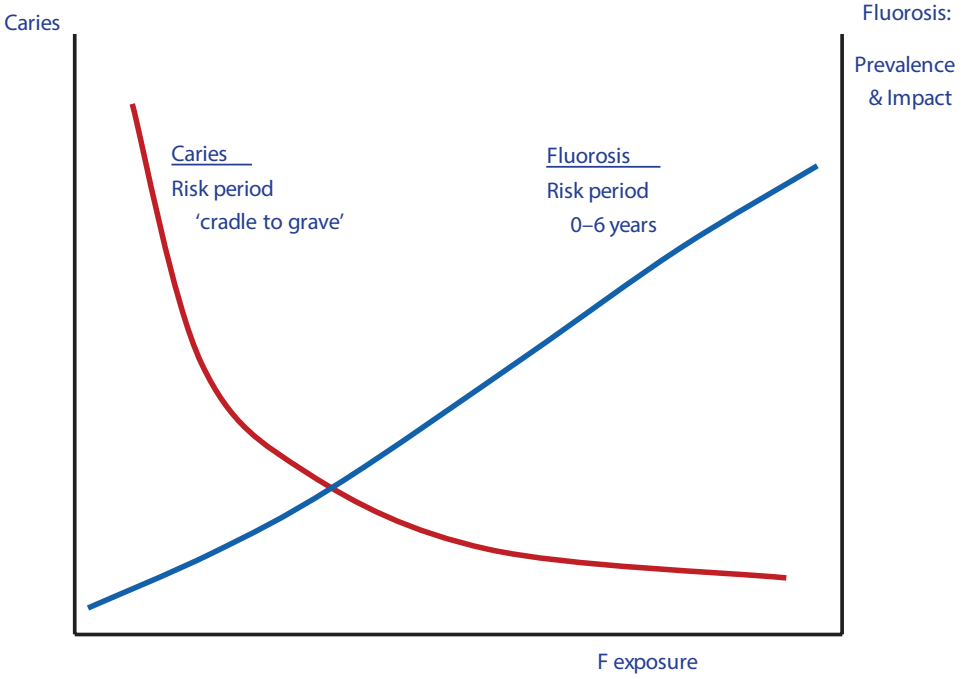


Fig. 7.1 Schematic description of the relationship between fluoride exposure, dental caries and fluorosis

ically normal but is more porous, i.e. the intercrystalline space is larger than normal. The degree and extent of porosity characterise the clinical appearance of fluorotic enamel, and it depends on the concentration of fluoride in the tissue fluids during the tooth development [1].

The mild form of fluorosis appears as white lines along the perikymata, which may merge to form irregular areas. With increasing severity, the affected area is larger and can cover the whole surface of the tooth. Severe fluorosis may be characterised with brownish staining and even minute pitting on the enamel surface. These features are mostly posteruptive changes [1].

Mild fluorotic lesions often affect the whole tooth surface and may be more visible on or near the tip of cusps/incisal edges. The fluorotic lesion is a diffuse discolouration without clear demarcation with normal enamel. Fluorotic teeth erupt with an opaque white colour, or even chalky appearance. Another typical characteristic is that fluorosis always affects homologous pairs of teeth. These characteristics are used to differentiate mild forms of fluorosis from non-fluorotic lesions.

The mechanism underlying the development of enamel fluorosis has not been fully understood. There is general agreement that fluorotic enamel is formed during the period of enamel development. Fluoride is thought to affect the enamel formation process causing enamel porosity [2]. There is a clear linear relationship between fluoride exposure and severity of fluorosis. Despite extensive literature concerning the mechanism which leads to dental fluorosis, there are still unanswered questions. The most accepted concept is that the fluoride ion affects the early maturation phase by causing retention of intact and degraded proteins [4, 10]. Proteins, mainly amelogenins, are not completely removed from the enamel organ. The retention of proteins may explain the incomplete crystal growth that is observed in fluorotic enamel. Enamel developed under that condition may be characterised by greater intercrystalline space and hence is more porous.

7.1.2 Historical Trend of Dental Fluorosis

Dean [11] stated that some 12.2% of children living in areas with the optimal level of fluoride (1 ppm) had mild or very mild fluorosis. This percentage was around 1% in children from areas with negligible levels of fluoride in water. These data were collected when water was the only source of fluoride. They have served as the standard for the balance between the protective effect against caries and the risk of having fluorosis in population water fluoridation.

There have been dramatic changes in the second-half of the last century when fluoride was introduced in other forms. Water ceased to be the only source of fluoride. Studies around the world repeatedly reported a significant increase in the prevalence and severity of fluorosis among children.

A series of studies examining the prevalence of fluorosis reported an increase in the prevalence of fluorosis in both fluoridated and non-fluoridated areas in North America [12–18]. Although these studies employed different scoring methods, it was widely accepted that the prevalence and severity of fluorosis was on a sharp increase from the 1970s. The studies also provided evidence of a greater increase in fluorosis in non-fluoridated areas [16, 19]. The prevalence of fluorosis ranged from 4.4% to 55.0% in non-fluoridated areas and from 11.4% to 80.9% in fluoridated areas, with the majority of changes observed in the milder forms of the conditions [20]. The prevalence of fluorosis reported in European countries had a similar trend [21–24].

Rozier [25] reviewing studies of dental fluorosis in North American children pointed out an increase in the prevalence of fluorosis. The increasing trend was sharper in non-fluoridated areas, whereas the trend was less clear in fluoridated areas. The majority of fluorosis cases were mild, with around 1.3% of the US child population with moderate-to-severe fluorosis. The author suggested that individual behaviours were the main contributing factors to the increase in the prevalence of fluorosis.

Australia has seen a sharp increase in the prevalence of dental fluorosis in the 1980s–1990s [26, 27]. This trend was attributed to discretionary fluoride sources such as fluoride in infant formula powder, fluoride supplements and fluoride toothpaste [28–30]. Reduction in such fluoride sources has led to reduction in the prevalence and severity of dental fluorosis [31, 32]. The recent large population-based National Child Oral Health Study (NCOHS 2012–2014) reported that fluorosis in Australia children was predominantly very mild to mild (Table 7.1). The prevalence of moderate-to-severe fluorosis (TF score of 4 or higher) was 0.1% in both fluoridated and non-fluoridated areas. It is important to note that around 80% of the Australian children lived in fluoridated areas, and low concentration fluoridated toothpaste was used by the majority of the children. Such finding indicates significant role of fluoridated toothpaste in development of dental fluorosis, similar to findings reported by other studies [33, 34]. Some other small studies in a number of European countries reported varying prevalence of dental fluorosis using the TF Index. The prevalence of fluorosis at the TF score of 3+ was mostly low in both fluoridated and non-fluoridated areas. Studies in the USA using the Dean Index also reported low prevalence of moderate-to-severe fluorosis. The New Zealand National Oral Health Survey also reported low prevalence of moderate-to-severe fluorosis in both fluoridated and non-fluoridated areas.

Table 7.1 Prevalence and severity of dental fluorosis measured by the TF or the Dean Index in different regions

Study/year	Location (sample size)	Fluoridation status	Fluorosis severity, % (95% CI)[a]		
Data using the TF Index			*TF 1*	*TF 2*	*TF 3+*
Do and Spencer 2012–2014	Australia (10,369)	F	14.4 (12.9–15.8)	5.1 (4.4–5.8)	1.1 (0.9–1.4)
Do and Spencer 2012–2014	Australia (5228)	NF	5.6 (4.7–6.5)	2.2 (1.7–2.7)	0.4 (0.2–0.5)
Pretty et al. [24] 2015	Manchester, UK (466)	NF	33	3	2
Pretty et al. [24] 2015	Liverpool, UK (473)	NF	30	3	2
Pretty et al. [24] 2015	Newcastle, UK (510)	F	42	11	9
Pretty et al. [24] 2015	Birmingham, UK (450)	F	39	11	2.8
Cochran et al. [47] 2002	Cork, Ireland (325)	F	59	26	4
Cochran et al. [47] 2002	Knowsley, UK (314)	NF	54	11	1
Cochran et al. [47] 2002	Oulu, Finland (315)	NF	61	21	0
Cochran et al. [47] 2002	Athens, Greece (283)	NF	48	5	0
Cochran et al. [47] 2002	Reykjavik, Iceland (296)	NF	51	16	1
Cochran et al. [47] 2002	Haarlem, Netherland (303)	NF	54	22	4
Cochran et al. [47] 2002	Almada/Setubal, Portugal, (210)	NF	43	7	1
Data using the Dean Index			*Very mild*	*Mild*	*Moderate/severe*
Beltran et al. [35] 1986–1987	US NIDR (NA)	Varied	17.2 (12.1–22.2)	4.1 (2.9–5.7)	1.3 (0.6–1.5)
Beltran et al. [35] 1999–1904	US NHANES (NA)	Varied	28.5 (25.8–32.3)	8.6 (7.0–10.3)	3.6 (2.5–4.5)
NZ MoH 2009	NZ (NA)	F	10.2 (5.5–16.9)	3.0 (0.8–7.6)	1.7 (0.3–5.5)
NZ MoH 2009	NZ (NA)	NF	10.3 (5.7–16.8)	7.8 (4.3–12.7)	2.3 (0.5–6.8)

[a]95% confident intervals of estimates. Not available in all studies

In general, the prevalence of dental fluorosis was on a sharp increase in the last three decades of the twentieth century. The increase was suggested to be a result of an introduction of numerous forms of fluoride available for children's use. The trend has reversed in countries and population where discretionary fluoride sources have been limited or eliminated.

7.1.3 Risk Factors for Dental Fluorosis

There is well-established agreement that dental fluorosis can occur only during the enamel development period. Therefore, any source of systemic fluoride available during the amelogenesis phase may pose a level of risk for the condition. Up to now, fluoride from water and beverages, fluoride supplements, dietary fluoride, fluoride

toothpaste and the number of topical fluoride applications are known sources of fluoride that can be available systemically during the enamel formation period [3, 33, 36]. The evidence of these sources as risk for fluorosis will be considered below.

7.1.3.1 Fluoridated Water

Fluoridated water had been the first controlled source of fluoride in the fight against dental caries. While the caries-protective effect of water fluoridation has been well documented [37–40], fluoride from water has also been a known risk for fluorosis.

When Dean conducted his path-finding studies, there was a difference found in the prevalence of dental fluorosis between areas with varying levels of fluoride. Residence in an area where fluoride in the water supply was around 1 ppm carried significantly higher risk for fluorosis compared to residence in an area with a negligible level of fluoride in water. The prevalence of mild to very mild fluorosis was about 18-fold higher in the former area compared to the latter. However, risk of having fluorosis in an optimally fluoridated area is now only twice as high compared to a non-fluoridated area. This phenomenon can be explained by the universal availability of fluoride from numerous sources such as fluoride supplements, fluoride toothpaste and dental products. Also, the so-called "diffusion" effect can occur, in that residents in a non-fluoridated area can be exposed to fluoride in foods and beverages that are produced in a fluoridated area and transported for consumption into that non-fluoridated area.

A number of published studies investigated water fluoridation as a risk factor for fluorosis [14, 18, 29, 41–44]. Griffin and co-workers [45] investigated the risk of having aesthetically objectionable fluorosis that could be attributable to water fluoridation using the Dean Index and the anterior index (a modification of the Dean Index applied for use on anterior teeth only). Using the anterior index, fluoridation was a risk factor for very mild (attributable risk = 15%) and mild fluorosis (attributable risk = 3%). The risk of fluorosis (very mild or greater) attributable to fluoridation using the Dean Index was 24%. The authors concluded that approximately 2% of US schoolchildren might experience a perceived aesthetic problem related to dental fluorosis which could be attributed to water fluoridation. Do and Spencer, evaluating risk and benefit trade-off of exposure to water fluoridation among Australian children, estimated some 55% of cases of fluorosis with a TF score of 2 (very mild) or higher were attributed to early life exposure to fluoridated water [42]. The prevalence of more severe fluorosis (TF score of three or higher) was very low in that population.

7.1.3.2 Fluoride Toothpaste

One of the most popular sources of fluoride is fluoride toothpaste. Introduced in the 1970s, fluoride toothpastes consist of more than 90% of the toothpaste market in western countries [46]. Available in different forms and concentrations, fluoride toothpaste significantly contributes to the prevention of dental caries [47]. However, its use can be a risk factor for fluorosis as well [34]. Children can ingest an amount of fluoride from toothpaste that may well exceed the optimal daily intake [48, 49].

Recent studies reported a link between toothpaste and the prevalence and severity of fluorosis [30, 50]. Some studies found that early use of toothpaste was a risk factor for fluorosis [51, 52]. Another study reported higher frequency of brushing with toothpaste as a risk indicator for fluorosis [53].

Studies that calculated adjusted attributable risk also found factors linked to toothpaste use as risk factors for fluorosis. A study among Western Australian children living in a fluoridated area reported that 47% of fluorosis cases were attributed to swallowing toothpaste in infancy [27]. Another study [53] reported that 72% of fluorosis cases could be explained by commencement of tooth brushing in the first 2 years of life. Using more than a pea-sized amount of toothpaste more than once per day in a fluoridated population attributed to 46% of fluorosis cases, whereas brushing more than once per day in the first 2 years of life by children in non-fluoridated areas explained a third of fluorosis cases [30]. Do and Spencer estimated that using standard 1000-ppm toothpaste in early age and eating toothpaste attributed to over 60% of cases with fluorosis (TF score of 2 or higher) in Australian child population [42].

There are recommendations to reduce fluoride intake from fluoridated toothpaste by using a lower concentration of fluoride toothpaste and implementing stricter guidelines for its use [46]. Low concentration fluoride toothpaste is available for use in a number of countries including European nations and Australia. Its use was reportedly linked with a lower prevalence of fluorosis among children [31, 32].

7.1.3.3 Fluoride Supplements

Fluoride supplements have been used to prevent dental caries in children for more than half a century. They are available in the form of tablets, drops or lozenges. These supplements are recommended for children living in fluoride-deficient places. Dosage schemes are available to guide their use based on the age of the child and on the fluoride level of drinking water [54–56]. However, evidence is available that fluoride supplements are prescribed to children without taking into account the level of fluoride in drinking water [30]. Supplement use has been linked with low compliance with recommended dosage schedules [57].

Numerous studies identified fluoride supplement use as a risk factor for fluorosis both in fluoridated and fluoride-deficient areas [3, 33, 58]. Therefore, the risk of fluoride supplement use for having fluorosis is well confirmed. Recommendations were made to reduce the

available dosage schedule [59] as well as eliminate fluoride supplement use in children [60]. These recommendations were incorporated into national guidelines for fluoride use [61, 62].

7.1.3.4 Fluoride from Foods

Children can be exposed to differing levels of fluoride available from their diet during the tooth formation period. Various foods have been found to contain varying amounts of fluoride [63–66]. Several infant foods were also found to have high levels of fluoride, such as mechanically processed chicken or food sources in a number of African populations [67, 68]. However, those sources of fluoride are not available to the general population in western countries.

In the last decade, infant formula was often found to have high levels of fluoride and could potentially be responsible for a certain proportion of fluorosis in children [30, 69]. In Australia before the 1990s, the fluoride content of milk-based formula ranged from 0.23 to 3.71 and for soy-based formula from 1.08 to 2.86 micrograms of fluoride in a gram of powder [70]. Infant formula was earlier considered a risk factor for fluorosis in but that has changed after manufacturers' reduction of fluoride level in formula powder [33, 71] [31, 41, 72].

7.1.4 The Measurement of Dental Fluorosis

7.1.4.1 Approaches in the Measurement of Fluorosis

Enamel fluorosis is a developmental defect of the tooth appearance. It is one of numerous discolourations observed on the tooth's enamel surface. Instruments available to record such developmental changes of enamel can be divided into descriptive and fluorosis-specific indices. The descriptive indices do not specifically diagnose fluorosis but rather describe the appearance of discolouration on the tooth surface. They include the Developmental Defects of Enamel (DDE) Index [73], Murray-Shaw Index [74] and Al-Alousi Index [75]. Among these indices, the DDE Index is the most commonly used. These indices, however, do not allow for estimation of the prevalence of dental fluorosis. Therefore, they are not relevant instruments for this study, which investigated fluoride-related development changes.

The fluorosis-specific indices initially diagnose dental fluorosis and then record it according to a range of severity levels. These indices are the Dean Index [11, 76], the Thylstrup and Fejerskov (TF) Index [77], the Tooth Surface Index of Fluorosis (TSIF) [78] and the Fluorosis Risk Index (FRI) [79]. These indices are more relevant to the epidemiological evaluation of dental fluorosis and will be discussed in more details.

7.1.4.2 Differential Diagnosis of Fluorosis

Clinical diagnosis of mild form of enamel fluorosis is often problematic owing to similarities in its appearance with other non-fluorotic enamel conditions [80]. In order to document the presence/absence of fluorosis in a person and/or an individual tooth, a differential diagnosis of the condition is required. The differential diagnosis is based on specific characteristics of fluorotic lesions such as bilateral symmetry, colour or shape of lesion. The criteria developed by Russell [80] and presented in Table 7.2 are the most widely accepted.

Table 7.2 Differential diagnostic criteria *for dental fluorosis* [80]

Characteristics	Dental fluorosis	Enamel opacities
Area affected	The entire tooth surfaces (all surfaces) often enhanced on or near tips of cusp/ incisal edge	Usually centred in smooth surface of limited extent
Lesion shape	Resemble line shading in pencil sketch, which follow incremental lines in enamel (perikymata). Lines merging and cloudy appearance. At cusp/incisal edges formation of irregular white caps ("snow cap")	Round or oval
Demarcation	Diffuse distribution over the surface of varying intensity	Clearly differentiated from adjacent normal enamel
Colour	Opaque white lines or clouds; even chalky appearance. "Snow cap" at cusp/incisal edge. Some lesions may become brownish discoloured at mesio-incisal part of central upper incisors after eruption	White opaque or creamy-yellow to dark reddish-orange at time of eruption
Teeth affected	Always on homologous teeth. Early erupting teeth (incisors/first molars) least affected. Premolars and second molars (and third molars) most severely affected	Most common on labial surfaces of single or occasionally homologous teeth. Any teeth may be affected but mostly incisors

7.1.4.3 Fluorosis Indices Available

The Dean Index [76]

Dean had made a fundamental contribution to the assessment of dental fluorosis. While conducting his investigation of dental mottling, Dean recognised the value of a classification system for the clinical manifestation of the condition in answering several research questions. The questions to be addressed by Dean's efforts were aetiology and pathogenesis of dental fluorosis and its pattern in a population. Therefore, Dean developed a six-category index with the aim of describing the clinical manifestation of fluorosis and reflecting as closely as possible the biological effects of fluoride on tooth enamel. The description of the categories is shown in the Table 7.3.

This index has been a historically remarkable instrument in measuring fluorosis. It has been the most widely used index of fluorosis, especially in population descriptive studies. However, there are several limitations of the index that may affect its validity in relating fluorosis to sources of fluoride exposure and in risk assessment studies in light of the current knowledge of fluoride action. The index does not clearly identify histological characteristics of fluorotic enamel. It may incorrectly accept extrinsic discolouration as an indication of the severity of fluorosis. Also, the category "Questionable" is vaguely characterised. Therefore, diagnosis of fluorosis by the index may vary depending on the case definition chosen by investigators. On the other hand, as more severe fluorotic enamel is not classified in detail, its use may be limited where populations have more severe conditions.

Table 7.3 The Dean Index

Category	Description
Normal	The enamel surface is smooth, glossy and usually a pale creamy-white colour
Questionable	The enamel shows slight aberrations from the translucency of normal enamel, which may range from a few white flecks to occasional spots. This classification is used where the classification "normal" is not justified
Very mild	Small opaque paper-white areas scattered irregularly over the tooth but involving less than 25% of the labial tooth surface
Mild	The white opacity of the enamel of the teeth is more extensive than in category 2, but covers less than 50% of the tooth surface
Moderate	The enamel surface of the teeth shows marked wear, and brown stain is frequently a disfiguring feature
Severe	The enamel surface is badly affected, and hypoplasia is so marked that the general form of the tooth may be affected. There are pitted or worn areas, and brown stains are widespread; the teeth often have corroded appearance

The Thylstrup and Fejerskov (TF) Index [77]

The Thylstrup and Fejerskov (TF) Index assesses buccal surfaces of teeth using a 10-point scale (Table 7.4). This index was designed in the late 1970s with the aim of

Table 7.4 Criteria for the Thylstrup and Fejerskov (TF) Index

Category	Description
TF score 0	The normal translucency of the glossy creamy-white enamel remains after wiping and drying of the surface
TF score 1	Thin white opaque lines are seen running across the tooth surface. Such lines are found on all part of the surface. The lines correspond to the position of the perikymata. In some cases, a slight "snow-capping" of cusps/incisal edge may also be seen
TF score 2	The opaque white lines are more pronounced and frequently merge to form small cloudy areas scattered over the whole surface. "Snow-capping" of the incisal edges and cusp tip is common
TF score 3	Merging of the white lines occurs, and cloudy areas of opacity occur over many parts of the surface. In between the cloudy areas white lines can also be seen
TF score 4	The entire surface exhibits a marked opacity, or appears chalky white. Parts of the surface exposed to attrition or wear may appear to be less affected
TF score 5	The entire surface is opaque, and there are round pits (focal loss of the outermost enamel) that are less than 2 mm in diameter
TF score 6	The small pits may frequently be seen merging in the opaque enamel to form bands that are less than 2 mm in vertical height. In this class are included also surfaces where the cuspal rim of facial enamel has been chipped off, and the vertical dimension of the resulting damage is less than 2 mm
TF score 7	There is a loss of the outermost enamel in irregular areas, and less than half of the surface is so involved. The remaining intact enamel is opaque
TF score 8	The loss of the outermost enamel involves more than half of the enamel. The remaining intact enamel is opaque.
TF score 9	The loss of major part of the outer enamel results in a change of the anatomical shape of the surface/tooth. A cervical rim of opaque enamel is often noted.

classifying the clinical features of fluorosis reflecting the histological changes in enamel in association with differing degrees of fluorosis severity. The index was based on histological and electron microscopic characteristics of fluorotic enamel. Several clinical manifestations such as discolouration and surface pitting were considered as posteruptive and were subsequently taken into account in the design of the index.

One of the advantages of this index is that it distinctively identifies fluorosis, especially milder forms of fluorosis, from other non-fluorotic discolourations. The requirement for drying teeth before examination increases the capability of the index to identify teeth with fluorosis. The assessment can be made for any present teeth, which may facilitate the description of the intra-oral distribution of fluorosis. Comparability of data collected from different studies with a different number of examined teeth is also feasible provided the same tooth (or group of teeth) is to be compared. These features have made the TF Index one of the methods of choice in studying the prevalence and severity of dental fluorosis.

The Fluorosis Risk Index (FRI) [79]

The FRI features a scoring system of different zones of a tooth surface. It divides tooth surfaces into four surface zones: occlusal/incisal edge; incisal one-third; middle one-third; and cervical one-third [79]. The index then divides the surface zones into two distinctive classifications based on their time of mineralisation: classification I zones are 10 surface zones that are mineralised in the first year of life; classification II zones are 48 zones that are mineralised during the third year through to the sixth year of life. Surface zones that are mostly mineralised during the second year after birth are not included in the classification system for the index. This makes the two classifications more distinctive from each other. The rationale for this classification was that different fluoride exposures may have different effects on fluorosis experience on surface zones that are mineralised at different times during an individual's life. The surface zones of the two classifications are presented in Table 7.5.The diagnostic criteria for fluorosis used in this index are shown in Table 7.6.

The Tooth Surface Index of Fluorosis (TSIF) [78]

The Tooth Surface Index of Fluorosis (TSIF) was designed to record fluoride-related conditions on different tooth surfaces (Table 7.7). It consists of a 7-point scale based on the area affected and the presence of discolouration and pitting. The biological effect of fluoride on tooth enamel, however, is less emphasised in this index. It may, therefore, be less sensitive to changes in fluorosis severity because of different levels of fluoride exposure.

Table 7.5 Surface zone classifications by the FRI

Tooth number	7	6	5	4	3	2	1
Upper teeth							
Occlusal/incisal edge	C2	C1	C2	C2			C1
Incisal 1/3	C2		C2	C2			
Middle 1/3	C2		C2	C2	C2		
Cervical 1/3						C2	C2
Lower teeth							
Occlusal /incisal edge	C2	C1	C2	C2		C1	C1
Incisal 1/3	C2		C2	C2			
Middle 1/3	C2		C2	C2	C2		
Cervical 1/3						C2	C2

C1: classification I surface zone
C2: classification II surface zone
Blank: not classified surface zones

Table 7.6 Criteria for the Fluorosis Risk Index (FRI)

Category	Description
Negative finding	
Score 0	A surface zone will receive a score of 0 when there is absolutely no indication of fluorosis being present. There must be a complete absence of any white spots or striations, and tooth surface colouration must appear normal
Questionable finding	
Score 1	Any surface zone that is questionable as to whether there is fluorosis present (i.e. white spots, striations or fluorotic defects cover 50% or less of the surface zone) should be score as 1
Score 7	Any surface zone that has an opacity that appears to be a non-fluoride opacity should be score as 7
Positive finding	
Score 2	A smooth surface zone will be diagnosed as being positive for enamel fluorosis if greater than 50% of the zone displays parchment-white striations typical of enamel fluorosis. Incisal edges and occlusal tables will be scored as positive for enamel fluorosis if greater than 50% of that surface is marked by the snow-capping typical of enamel fluorosis
Score 3	A surface zone will be diagnosed as positive for severe fluorosis if greater than 50% of the zone displays pitting, staining and deformity, indicative of severe fluorosis.

Table 7.6 (continued)

Category	Description
Surface zone excluded	
Score 9	A surface zone is categorised as excluded (i.e. not adequately visible for a diagnosis to be made) when any of the following conditions exist: Incomplete eruption Rule 1: If a tooth is in proximal contact but the occlusal surface is not parallel with existing occlusion, the occlusal two-thirds of the tooth are scored, but the cervical one-third is recorded as excluded Rule 2: If a tooth is erupted, but not yet in contact, the incisal/occlusal edge is scored, but all other surfaces are recorded as excluded Orthodontic appliances and bands Rule 1: If there is an orthodontic band present on a tooth, only the occlusal table or incisal edge should be scored Rule 2: If greater than 50% of the surface zones are banded, the surface should be recorded as excluded Surface crowned or restored Rule: Surface zones that are replaced by either a crown or restoration covering greater than 50% of the surface zone should be recorded as excluded Gross plaque and debris Rule: Any subject with gross deposits of plaque or debris on greater than 50% of the surface zones should be excluded from examination

Table 7.7 The Tooth Surface Index of Fluorosis (TSIF)

Numerical score	Descriptive criteria
0	Enamel shows no evidence of fluorosis
1	Enamel shows definite evidence of fluorosis, namely, areas with parchment-white colour that total less than one-third of the visible enamel surface. This category includes fluorosis confined only to incisal edges of anterior teeth and cusp tips of posterior teeth ("snow-capping")
2	Parchment-white fluorosis totals at least one-third of the visible surface but less than two-thirds
3	Parchment-white fluorosis totals at least two-third of the visible surface
4	Enamel shows staining in conjunction with any of the preceding levels of fluorosis. Staining is defined as an area of definite discolouration that may range from light to very dark brown
5	Discrete pitting of the enamel exists, unaccompanied by evidence of staining of intact enamel. A pit is defined as a definite physical defect in the enamel surface with a rough floor that is surrounded by a wall of intact enamel. The pitted area is usually stained or differs in colour from the surrounding enamel
6	Both discrete pitting and staining of the intact enamel exist
7	Confluent pitting of the enamel surface exists. Large areas of enamel may be missing, and the anatomy of the tooth may be altered. Dark-brown stain is usually present

7.1.5 Public Opinion on Fluorosis

Public opinion is an important feedback mechanism for policies on fluoride use. When dental caries was endemic in western countries in the middle of the last century [81], the public opinion focused on finding effective prevention. However, when population oral health improved, attention turned to fluorosis [82]. Early research on public opinion about fluorosis often focused on perception of appearance [83]. Research considered effect of fluorosis on perception of oral health-related quality of life [84, 85] that made it easier to define health effect of fluorosis.

Mild fluorosis was found to be discernible by children and their parents. The impact of mild fluorosis on the perception of dental appearance, however, was less pronounced in this child population. Some fluorosis was tantamount to lower caries experience – the other side of the balance of risk and benefit of fluoride use. Caries experience seemed to have a more pronounced impact by causing more oral symptoms and functional limitations. Children and their parents who had mild fluorosis were even better off in terms of emotional well-being and social well-being when other factors were controlled for in multivariate models. This rather unexpected finding might be explained by the fact that better oral health was often perceived as being without caries. The psychological impact of fluorosis on the perception of dental appearance, if any, was outweighed by a feeling of being free from the impact of caries.

A longitudinal study of dental fluorotic lesions reported that mild fluorosis diminished with time [86]. This finding is highly important in epidemiological evaluation of dental fluorosis and its impact on oral health of the populations of interest.

Final Considerations

This chapter summarises the epidemiological aspects of dental fluorosis. Aetiology, histological features of fluorotic lesions and indices of measurement have been presented and discussed. Information on risk factors and time trend inform appropriate measures to be considered. Dental fluorosis is an important oral epidemiological condition. Understanding epidemiological aspects of this condition and its impact on population oral health informs relevant policies and practices in using fluoride for preventing dental caries.

References

1. Fejerskov O, Manji F, Baelum V. The nature and mechanisms of dental fluorosis in man. J Dent Res. 1990;69 Spec No:692–700; discussion 721.
2. Fejerskov O, Larsen MJ, Richards A, Baelum V. Dental tissue effects of fluoride. Adv Dent Res. 1994;8:15–31.
3. Levy SM. An update on fluorides and fluorosis. J Can Dent Assoc. 2003;69:286–91.
4. Aoba T, Fejerskov O. Dental fluorosis: chemistry and biology. Crit Rev Oral Biol Med. 2002;13:155–70.
5. Evans RW, Darvell BW. Refining the estimate of the critical period for susceptibility to enamel fluorosis in human maxillary central incisors. J Public Health Dent. 1995;55:238–49.
6. Bardsen A. "Risk periods" associated with the development of dental fluorosis in maxillary permanent central incisors: a meta-analysis. Acta Odontol Scand. 1999;57:247–56.
7. Den Besten PK. Mechanism and timing of fluoride effects on developing enamel. J Public Health Dent. 1999;59:247–51.
8. Fejerskov O, Johnson NW, Silverstone LM. The ultrastructure of fluorosed human dental enamel. Scand J Dent Res. 1974;82:357–72.
9. Thylstrup A. A scanning electron microscopical study of normal and fluorotic enamel demineralized by EDTA. Acta Odontol Scand. 1979;37:127–35.
10. Robinson C, Connell S, Kirkham J, Brookes SJ, Shore RC, Smith AM. The effect of fluoride on the developing tooth. Caries Res. 2004;38:268–76.
11. Dean HT. The investigation of physiological effects by the epidemiological method. In: Moulton F, editor. Fluorine and dental health. Washington, D.C.: American Association for the Advancement of Science; 1942.
12. Driscoll WS, Horowitz HS, Meyers RJ, Heifetz SB, Kingman A, Zimmerman ER. Prevalence of dental caries and dental fluorosis in areas with optimal and above-optimal water fluoride concentrations. J Am Dent Assoc. 1983;107:42–7.
13. Driscoll WS, Horowitz HS, Meyers RJ, Heifetz SB, Kingman A, Zimmerman ER. Prevalence of dental caries and dental fluorosis in areas with negligible, optimal, and above-optimal fluoride concentrations in drinking water. J Am Dent Assoc. 1986;113:29–33.
14. Ismail AI, Brodeur JM, Kavanagh M, Boisclair G, Tessier C, Picotte L. Prevalence of dental caries and dental fluorosis in students, 11–17 years of age, in fluoridated and non-fluoridated cities in Quebec. Caries Res. 1990;24:290–7.
15. Ismail AI, Messer JG, Hornett PJ. Prevalence of dental caries and fluorosis in seven- to 12-year-old children in northern Newfoundland and Forteau, Labrador. J Can Dent Assoc. 1998;64:118–24.
16. Leverett D. Prevalence of dental fluorosis in fluoridated and nonfluoridated communities – a preliminary investigation. J Public Health Dent. 1986;46:184–7.
17. Szpunar SM, Burt BA. Trends in the prevalence of dental fluorosis in the United States: a review. J Public Health Dent. 1987;47:71–9.
18. Heller KE, Eklund SA, Burt BA. Dental caries and dental fluorosis at varying water fluoride concentrations. J Public Health Dent. 1997;57:136–43.
19. Pendrys DG, Stamm JW. Relationship of total fluoride intake to beneficial effects and enamel fluorosis. J Dent Res. 1990;69 Spec No:529–38; discussion 556–7.
20. Clark DC. Trends in prevalence of dental fluorosis in North America. Community Dent Oral Epidemiol. 1994;22:148–52.
21. Clarkson JJ, O'Mullane DM. Prevalence of enamel defects/fluorosis in fluoridated and non- fluoridated areas in Ireland. Community Dent Oral Epidemiol. 1992;20:196–9.
22. Wenzel A, Thylstrup A. Dental fluorosis and localized enamel opacities in fluoride and nonfluoride Danish communities. Caries Res. 1982;16:340–8.
23. Woltgens JH, Etty EJ, Nieuwland WM, Lyaruu DM. Use of fluoride by young children and prevalence of mottled enamel. Adv Dent Res. 1989;3:177–82.
24. Pretty IA, Boothman N, Morris J, MacKay L, Liu Z, McGrady M, Goodwin M. Prevalence and severity of dental fluorosis in four English cities. Community Dent Health. 2016;33:292–6.
25. Rozier RG. The prevalence and severity of enamel fluorosis in North American children. J Public Health Dent. 1999;59:239–46.
26. Puzio A, Spencer A, Brennan D. Fluorosis and fluoride exposure in South Australian children. In: Consensus conference: appropriate fluoride exposure for infants and children. Perth: Department of Health Services; 1993.
27. Riordan PJ. Dental fluorosis, dental caries and fluoride exposure among 7-year-olds. Caries Res. 1993;27:71–7.
28. Riordan PJ. Fluoride supplements for young children: an analysis of the literature focusing on benefits and risks. Community Dent Oral Epidemiol. 1999;27:72–83.
29. Riordan PJ, Banks JA. Dental fluorosis and fluoride exposure in Western Australia. J Dent Res. 1991;70:1022–8.
30. Pendrys DG. Risk of enamel fluorosis in nonfluoridated and optimally fluoridated populations: considerations for the dental professional. J Am Dent Assoc. 2000;131:746–55.
31. Do LG, Spencer AJ. Decline in the prevalence of dental fluorosis among South Australian children. Community Dent Oral Epidemiol. 2007;35:282–91.
32. Riordan PJ. Dental fluorosis decline after changes to supplement and toothpaste regimens. Community Dent Oral Epidemiol. 2002;30:233–40.
33. Pendrys DG, Katz RV. Risk of enamel fluorosis associated with fluoride supplementation, infant formula, and fluoride dentifrice use. Am J Epidemiol. 1989;130:1199–208.
34. Wong MC, Glenny AM, Tsang BW, Lo EC, Worthington HV, Marinho VC. Topical fluoride as a cause of dental fluorosis in children. Cochrane Database Syst Rev. 2010;(1):CD007693.
35. Beltran-Aguilar ED, Barker L, Dye BA. Prevalence and severity of dental fluorosis in the United States, 1999–2004. NCHS Data Brief. 2010;(53):1–8.
36. Ophaug R, Singer L. Fluoride intake of infants and young children and the effect of supplemental and nondietary sources of fluoride. Compendium. 1988;9:68, 70–2, 74–5.
37. McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J, Misso K, Bradley M, Treasure E, Kleijnen J. Systematic review of water fluoridation. BMJ. 2000;321:855–9.

38. Newbrun E. Effectiveness of water fluoridation. J Public Health Dent. 1989;49:279–89.
39. NHMRC. Information paper – water fluoridation: dental and other human health outcomes. Canberra: National Health and Medical Research Council; 2017.
40. Rugg-Gunn AJ, Do L. Effectiveness of water fluoridation in caries prevention. Community Dent Oral Epidemiol. 2012;40(Suppl 2):55–64.
41. Do LG, Miller J, Phelan C, Sivaneswaran S, Spencer AJ, Wright C. Dental caries and fluorosis experience of 8-12-year-old children by early-life exposure to fluoride. Community Dent Oral Epidemiol. 2014;42:553–62.
42. Do LG, Spencer AJ. Risk-benefit balance in the use of fluoride among young children. J Dent Res. 2007;86:723–8.
43. Spencer AJ, Do LG. Changing risk factors for fluorosis among South Australian children. Community Dent Oral Epidemiol. 2008;36:210–8.
44. Szpunar SM, Burt BA. Dental caries, fluorosis, and fluoride exposure in Michigan schoolchildren. J Dent Res. 1988;67: 802–6.
45. Griffin SO, Beltran ED, Lockwood SA, Barker LK. Esthetically objectionable fluorosis attributable to water fluoridation. Community Dent Oral Epidemiol. 2002;30:199–209.
46. Horowitz HS. The need for toothpastes with lower than conventional fluoride concentrations for preschool-aged children. J Public Health Dent. 1992;52:216–21.
47. Marinho VC, Higgins JP, Sheiham A, Logan S. Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2003;1:CD002278.
48. Cochran JA, Ketley CE, Duckworth RM, van Loveren C, Holbrook WP, Seppa L, Sanches L, Polychronopoulou A, O'Mullane DM. Development of a standardized method for comparing fluoride ingested from toothpaste by 1.5–3.5-year-old children in seven European countries. Part 2: ingestion results. Community Dent Oral Epidemiol. 2004;32 Suppl 1: 47–53.
49. Rock WP, Sabieha AM. The relationship between reported toothpaste usage in infancy and fluorosis of permanent incisors. Br Dent J. 1997;183:165–70.
50. Mascarenhas AK, Burt BA. Fluorosis risk from early exposure to fluoride toothpaste. Community Dent Oral Epidemiol. 1998;26:241–8.
51. Maupome G, Shulman JD, Clark DC, Levy SM. Sociodemographic features and fluoride technologies contributing to higher fluorosis scores in permanent teeth of Canadian children. Caries Res. 2003;37:327–34.
52. Pendrys DG, Katz RV, Morse DE. Risk factors for enamel fluorosis in a nonfluoridated population. Am J Epidemiol. 1996;143:808–15.
53. Pendrys DG, Katz RV, Morse DE. Risk factors for enamel fluorosis in a fluoridated population. Am J Epidemiol. 1994;140: 461–71.
54. Dowell TB, Joyston-Bechal S. Fluoride supplements – age related dosages. Br Dent J. 1981;150:273–5.
55. Driscoll WS, Horowitz HS. Dosage recommendations for dietary fluoride supplements. Am J Dis Child. 1979;133:683–4.
56. CDC. CDC fluoride guidelines. Dent Assist. 2003;72:43.
57. Riordan PJ. The place of fluoride supplements in caries prevention today. Aust Dent J. 1996;41:335–42.
58. Ismail AI, Hasson H. Fluoride supplements, dental caries and fluorosis: a systematic review. J Am Dent Assoc. 2008;139: 1457–68.
59. Rozier RG, Adair S, Graham F, Iafolla T, Kingman A, Kohn W, Krol D, Levy S, Pollick H, Whitford G, Strock S, Frantsve-Hawley J, Aravamudhan K, Meyer DM. Evidence-based clinical recommendations on the prescription of dietary fluoride supplements for caries prevention: a report of the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 2010;141:1480–9.
60. Burt BA. The case for eliminating the use of dietary fluoride supplements for young children. J Public Health Dent. 1999;59:269–74.
61. ARCPOH. The use of fluorides in Australia: guidelines. Aust Dent J. 2006;51:195–9.
62. CDC. Recommendations for using fluoride to prevent and control dental caries in the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2001;50: 1–42.
63. Fomon SJ, Ekstrand J, Ziegler EE. Fluoride intake and prevalence of dental fluorosis: trends in fluoride intake with special attention to infants. J Public Health Dent. 2000;60:131–9.
64. Levy SM, Warren JJ, Broffitt B. Patterns of fluoride intake from 36 to 72 months of age. J Public Health Dent. 2003;63:211–20.
65. Levy SM, Warren JJ, Broffitt B, Hillis SL, Kanellis MJ. Fluoride, beverages and dental caries in the primary dentition. Caries Res. 2003;37:157–65.
66. Levy SM, Warren JJ, Davis CS, Kirchner HL, Kanellis MJ, Wefel JS. Patterns of fluoride intake from birth to 36 months. J Public Health Dent. 2001;61:70–7.
67. Awadia AK, Bjorvatn K, Birkeland JM, Haugejorden O. Weaning food and magadi associated with dental fluorosis in Northern Tanzania. Acta Odontol Scand. 2000;58:1–7.
68. Yoder KM, Mabelya L, Robison VA, Dunipace AJ, Brizendine EJ, Stookey GK. Severe dental fluorosis in a Tanzanian population consuming water with negligible fluoride concentration. Community Dent Oral Epidemiol. 1998;26:382–93.
69. Mascarenhas AK. Risk factors for dental fluorosis: a review of the recent literature. Pediatr Dent. 2000;22:269–77.
70. Silva M, Reynolds EC. Fluoride content of infant formulae in Australia. Aust Dent J. 1996;41:37–42.
71. Pendrys DG, Katz RV. Risk factors for enamel fluorosis in optimally fluoridated children born after the US manufacturers' decision to reduce the fluoride concentration of infant formula. Am J Epidemiol. 1998;148:967–74.
72. Spencer AJ and Do LG. Changing risk factors for fluorosis among South Australian children. Community Dent Oral Epidemiol. 2006;36(3):210–8.
73. Clarkson J, O'Mullane D. A modified DDE index for use in epidemiological studies of enamel defects. J Dent Res. 1989;68: 445–50.
74. Murray JJ, Shaw L. Classification and prevalence of enamel opacities in the human deciduous and permanent dentitions. Arch Oral Biol. 1979;24:7–13.
75. Al-Alousi W, Jackson D, Compton G, Jenkins OC. Enamel mottling in a fluoride and in a non-fluoride community. A study. Br Dent J. 1975;138:56–60.
76. Dean HT. Classification of mottled enamel diagnosis. J Am Dent Assoc. 1934;21:1421–6.
77. Fejerskov O, Manji F, Baelum V. Dental fluorosis: a handbook for health workers. Copenhagen: Munksgaard; 1988. p. 123.
78. Horowitz HS, Driscoll WS, Meyers RJ, Heifetz SB, Kingman A. A new method for assessing the prevalence of dental fluorosis – the tooth surface index of fluorosis. J Am Dent Assoc. 1984;109:37–41.
79. Pendrys DG. The fluorosis risk index: a method for investigating risk factors. J Public Health Dent. 1990;50:291–8.
80. Russell AL. The differential diagnosis of fluoride and nonfluoride enamel opacities. J Public Health Dent. 1961;21:143–6.
81. Do LG. Distribution of caries in children: variations between and within populations. J Dent Res. 2012;91:536–43.
82. Pendrys DG. Dental fluorosis in perspective. J Am Dent Assoc. 1991;122:63–6.

83. Riordan PJ. Perceptions of dental fluorosis. J Dent Res. 1993;72:1268–74.
84. Chankanka O, Levy SM, Warren JJ, Chalmers JM. A literature review of aesthetic perceptions of dental fluorosis and relationships with psychosocial aspects/oral health-related quality of life. Community Dent Oral Epidemiol. 2010;38:97–109.
85. Do LG, Spencer A. Oral health-related quality of life of children by dental caries and fluorosis experience. J Public Health Dent. 2007;67:132–9.
86. Do L, Spencer A, Ha D. Natural history and impact of dental fluorosis- a prospective cohort study. Med J Aust. 2016;18:204(1):25.

Traumatic Dental Injuries

Carlos Alberto Feldens, Fernando Freitas Portella, and Paulo Floriani Kramer

Contents

8.1 Introduction – 134

8.2 Preliminary Concepts – 134
8.2.1 Outcomes in Dental Traumatology – 134
8.2.2 Study Designs and Measures of Frequency in Dental Traumatology – 135
8.2.3 Etiology, Inferential Analysis, and Measures of Effect in Dental Traumatology – 137

8.3 Epidemiology in Dental Traumatology – 138
8.3.1 Prevalence and Distribution of TDI in Primary Teeth – 138
8.3.2 Prevalence and Distribution of TDI in Permanent Teeth – 140
8.3.3 Factors Associated with TDI in Permanent and Primary Teeth – 143

8.4 Impact of TDI – 149
8.4.1 Impact of TDI in Primary Teeth on OHRQoL – 149
8.4.2 Impact of TDI in Permanent Teeth on OHRQoL – 150

8.5 Interventions in Dental Traumatology – 151
8.5.1 Primary Prevention in Dental Traumatology – 152
8.5.2 Secondary and Tertiary Prevention in Dental Traumatology – 152

8.6 Conclusions – 153

References – 154

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_8

Overview

- TDI affects at least one fourth of preschoolers and approximately one fifth of schoolchildren and adolescents.
- The network of causality of TDI involves contextual and individual factors; the male gender and children/adolescents with accentuated overjet have consistently demonstrated risk factors, with psychosocial and behavioral characteristics also suggested.
- TDI exerts a negative impact on oral health-related quality of life in preschoolers, schoolchildren, and adolescents.
- Randomized clinical trials on TDI are scarce and pose a challenge for researchers; the obtainment of informed consent during immediate care as well as the diversity of tooth injuries and outcomes constitutes barriers to the development of prevention and treatment protocols.
- The prevention of TDI is based on identified risk factors; evidence suggests the need for health promotion actions directed at environmental and behavioral aspects as well as specific protection measures.
- Treatment for TDI is based on studies with moderate methodological quality, with few randomized clinical trials and systematic reviews of observational studies.

8.1 Introduction

Traumatic dental injuries (TDI) are challenging and passionate issues that have attracted the attention of oral health professionals and researchers, due to the fact that (a) the *prevalence* of this condition is high in childhood and adolescence, (b) it exerts an impact on *oral health-related quality of life (OHRQoL)*, and (c) medium-term and long-term treatment require costly, specialized, interdisciplinary care. From the clinical standpoint, this is a field in which health professionals perform some of their noblest functions, such as relieving pain and the reestablishment of both function and esthetics. From the point of view of researchers, few *risk factors* are known, making this an open field for research and hindering the planning of primary prevention strategies. Moreover, the emergency/urgent nature of TDI hinders the planning of randomized clinical trials, which means that treatment for different types of TDI is based on observational studies or case reports [1–3].

TDI affects different age groups from early childhood to adulthood. As the *prevalence*, etiology, *risk factors*, and even treatment can vary between dentitions, there is a clear division between studies addressing TDI in the primary and permanent dentitions. In practice, the fact that the anterior region is the most affected in all age groups means that studies on TDI in the primary dentition include children up to 6 years of age, whereas those on TDI in the permanent dentition involve children 6 years of age and older, adolescents, or adults.

In the present chapter, we perform an in-depth analysis of aspects related to the *prevalence*, impact, and *risk factors* of TDI in the primary and permanent dentitions from an epidemiological standpoint. We also highlight the challenges for future studies, particularly regarding the determination of prevention strategies and treatment.

8.2 Preliminary Concepts

8.2.1 Outcomes in Dental Traumatology

Unlike dental caries, which is a chronic disease that emerges after weeks, months, or even years of an imbalance in the demineralization-remineralization process and can progress in extension or vary in terms of activity, TDI occurs in a single moment and can affect different oral tissues with different degrees of extension. The adequate classification of tooth injuries is fundamental to the conduction of epidemiological studies, definition of the diagnosis, establishment of treatment, estimation of the prognosis, and determination of the necessary follow-up.

Several classifications have been used in the literature and by clinicians throughout the world [4]. The factors that determine the classification are etiology, anatomy, pathology, and therapeutic considerations [5]. In this chapter, we adopt the classification proposed by the World Health Organization and adopted by the International Association of Dental Traumatology (IADT) [6], which includes injuries to the tooth-supporting structures and fractures injuries (Table 8.1).

Epidemiological studies on TDI generally describe a portion of different types of tooth injury. However, frequency estimates or the investigation of *risk factors* generally uses the occurrence of any type of TDI as the outcome, grouping mild injuries, such as enamel fracture or concussion, with crown-root fracture or avulsion into a single category of a dichotomous variable (TDI: yes or no).

Regarding studies that have investigated the best treatment, a systematic review identified significant heterogeneity in the outcomes reported for TDI in the literature [7]. This demonstrates a lack of standardization with regard to outcomes in dental traumatology, which poses a challenge to researchers investigating this issue.

Table 8.1 Classification and definition of traumatic dental injuries [6]

TDI	Definition
Injuries to tooth-supporting structures	
Concussion	Injury to tooth-supporting structures without increased mobility or displacement of tooth but with pain upon percussion
Subluxation	Injury to tooth-supporting structures with increased mobility but without displacement of tooth. In acute trauma, bleeding from gingival sulcus confirms diagnosis
Extrusion	Partial displacement of tooth out of alveolar socket
Lateral luxation	Displacement of tooth other than axially. Displacement accompanied by comminution or fracture of either labial or palatal/lingual alveolar bone
Intrusion	Displacement of tooth into alveolar bone accompanied by comminution or fracture of alveolar socket
Avulsion	Complete displacement of tooth out of socket
Fracture injuries	
Enamel infraction	Incomplete fracture (crack) of enamel without loss of tooth structure
Enamel fracture	Fracture confined to enamel with loss of tooth structure
Uncomplicated crown fracture (enamel-dentin fracture)	Fracture confined to enamel and dentin with loss of tooth structure, but not involving pulp
Complicated crown fracture (enamel-dentin-pulp fracture)	Fracture involving enamel and dentin with loss of tooth structure and exposing pulp
Uncomplicated crown-root fracture	Fracture involving enamel, dentin, and cementum with loss of tooth structure, but not involving pulp
Complicated crown-root fracture	Fracture involving enamel, dentin, and cementum with loss of tooth structure and involving pulp
Root fracture	Fracture involving cementum, dentin, and pulp. Root fractures can be further classified by whether coronal fragment is displaced (see luxation injuries)
Alveolar fracture	Fracture of alveolar process may or may not involve alveolar socket

Source: IADT Dental Trauma Guide

Therefore, the IADT developed the "core outcome set" for TDI in both children and adults using the Delphi research method, the aim of which was to define how, when, and by whom these outcomes should be measured [8]. The following were the selected generic outcomes:

1. Periodontal healing (including bone loss, gingival recession, mobility, ankylosis, and resorption)
2. Pain
3. Discoloration
4. Tooth loss (including premature loss for primary teeth)
5. Quality of life (including days off work, school, or sports)
6. Esthetics (patient perception)
7. Trauma-related dental anxiety
8. Number of clinic visits

The implementation of standardized outcomes ensures that data from clinical studies and trials can be adequately compared, contrasted, and/or combined, leading to improved research outcomes [8].

8.2.2 Study Designs and Measures of Frequency in Dental Traumatology

Traditional epidemiological concepts of study designs and frequency measures also apply to TDI. However, some peculiarities should be considered.

Evidence-based prevention and treatment strategies for different conditions are best determined through randomized clinical trials (RCTs) or systematic reviews of randomized trials. However, TDI is an emergency condition, and the ethical issues related to obtaining informed consent from an injured child or adult to participate in an RCT constitute a challenge. This discourages dental researchers and practitioners from undertaking intervention studies involving patients with TDI [1, 9] and may at least partially explain the virtual nonexistence of randomized clinical trials and systematic reviews of randomized trials addressing TDI. The shared responsibility among different dental specialties in dental traumatology also makes RCTs complicated to plan and evaluate. Indeed, there are few plausible arguments for carrying out RCTs, which makes TDI a field in which the development of intervention studies with adequate methodological quality is almost prohibitive [6].

Thus, observational designs account for the vast majority of epidemiological studies in dental traumatology, particularly cross-sectional studies, which generally report the prevalence of TDI in a population and estimate *associated factors*. Cohort studies are less fre-

quent and generally report the *incidence* of TDI in a population and have the aim of estimating *risk factors* or prognoses [3]. Studies with a low power of evidence, such as narrative reviews and case reports, are published with considerable frequency in the international literature.

Regarding frequency measures, *prevalence* is the proportion of individuals in a population that have a condition (old or new cases) at a given time [10]. The *prevalence* of TDI in epidemiological studies normally involves records of signs that remained after the occurrence, such as a crown fracture or displacement. Most *prevalence* studies do not include root fracture or fractures of the bone tissue due to difficulties in obtaining radiographic data. Once dental trauma has occurred in a given individual, he/she will always be counted as a "prevalent case." Therefore, the concept that is most adequate for TDI is "lifetime *prevalence*,", which expresses the proportion of individuals who have suffered a tooth injury some time in life [11]. This knowledge is the basis for understanding why older children and adolescents generally have a greater *prevalence* of TDI in both dentitions. Rather than suggesting that age increases the risk of TDI, this finding merely regards the cumulative nature of this condition.

The *prevalence* of TDI can be compared between exposed and nonexposed individuals with regard to one or more variables, indicating *associated factors*.

EyeCatcher

Baxevanos et al. (2017) [12] investigated the association between TDI and psychosocial factors in adolescents aged 13–16 years. Among the 531 individuals examined, 84 exhibited dental trauma (prevalence: 15.8%). The *prevalence* of TDI was higher among adolescents reporting lower parental support than those with higher parental support.

Incidence is the proportion of individuals that experience one or more episodes of TDI (new cases) in a specific period of time [10]. Therefore, *incidence* expresses the frequency of new events in a population at risk of being affected by a condition in a longitudinal study. As a child is not exposed to TDI prior to being born, the frequency of TDI at 2 years of age is equivalent to the *incidence* of this condition in the first 2 years of life.

For TDI, a cohort may be comprised of a group of children with no previous history of trauma that will be followed up for a determined length of time to evaluate the *incidence* of events at different ages.

EyeCatcher

Borges et al. [13] followed a birth cohort of 458 children during preschool age in the city of Porto Alegre, Brazil. The children were examined at 3 years of age and 142 exhibited signs of TDI. In this case, the numerator is 142, and the denominator is 458, indicating a 31.0% *incidence* of TDI in the first 3 years of life. A significant difference was found between the genders, as the *incidence* was 36.5% (85/233) for boys and 25.3% (57/225) for girls.

A single study may follow two cohorts (one exposed and one nonexposed) to determine whether there is a difference in the *incidence* of trauma. In such cases, the study has the clear intention of determining whether the risk among the exposed individuals is greater than that among the nonexposed individuals, which enables establishing a relationship of causality. The major aim of cohort studies is precisely the comparison of the *incidence* of disease or events in two or more cohorts.

EyeCatcher

Ramos-Jorge et al. [14] accompanied 306 adolescents aged 11–13 years in a study involving a cohort of exposed individuals (those with previous TDI) and another of nonexposed individuals (those without previous TDI). After a 2-year follow-up period, the authors reported a greater incidence of TDI with the exposed adolescents (11.9%) compared to the nonexposed group (2.7%), indicating a greater risk of developing further dental trauma among adolescents with previous dental trauma.

A cohort may also be a group of individuals (or teeth) that share the fact of having suffered a particular trauma and will be followed up to determine the *incidence* of different consequences in the subsequent years. In such cases, the unit of analysis is often the tooth rather than the individual.

EyeCatcher

Hermann et al. [15] followed up 179 permanent teeth with lateral luxation in 149 patients. After 3 years, the incidence of repair-related resorption in teeth with immature root development was 2.1%, and the incidence of infection-related resorption was also 2.1%. For mature root development, the incidence of repair-related resorption and infection-related resorption was 29.5% and 2.6%, respectively.

In prospective cohort studies on TDI, the researcher follows the study population for a long enough time to enable the outcomes to occur.

EyeCatcher

Andreasen and Ravn (1971) [16] followed up 213 injured primary teeth in 103 patients to evaluate the effect on the permanent successors. In this case, exposure (TDI) had occurred at the beginning of the study, but the outcome (effect on permanent successor) occurs and is recorded in the future. The authors found that different exposures (characterized by different ages in which the trauma took place) were responsible for different incidences of effects on the permanent successors, demonstrating an association between the period of trauma and incidence of harm to the successor.

In retrospective cohort studies on TDI, which are often conducted with data collected from clinical charts, both exposure and outcome occurred prior to the onset of the study.

EyeCatcher

Holan and Ram (1999) [17] analyzed the clinical charts of 110 children who had suffered intrusion in 172 primary incisors and determined the sequelae that occurred due to the trauma. The authors concluded that the majority of incisors re-erupted and remained without complications for more than 36 months after the trauma, even in cases of intrusion of the entire crown. In this study, both exposure (intruded tooth) and the possible outcomes (re-eruption or post-trauma complication) had already occurred prior to the onset of the study.

When the record of TDI is based on the reports of parents and caregivers, studies have demonstrated significant errors in both the primary and permanent dentitions [18–20]. Studies in which the outcome is reported by parents/caregivers can record less than half of the injuries determined by a physical examination, corresponding to a high rate of measurement bias.

Another particularity of TDI is that the reported frequencies of different types of injury are strongly influenced by the setting in which the study is conducted. Studies involving representative samples or those with schoolchildren predominantly record the occurrence of tooth fractures, since these are generally the most visible signs, even if having been submitted to restorative treatment. In contrast, mild injuries to the supporting tissue, such as concussion and subluxation, generally go undiagnosed in such surveys.

Studies conducted at TDI services in clinics, dental schools, or hospitals generally report a greater frequency of injury to the supporting tissues. This is clearly characterized as an urgent situation for which there is a greater demand for treatment. Such circumstances largely explain the significant differences among studies regarding the distribution of different types of TDI. Therefore, an underestimation of the actual frequency of specific types of TDI can occur, depending on the methods employed in a study. Independently of the measure of frequency used, it should always refer to the dimensions of time, space, and population.

8.2.3 Etiology, Inferential Analysis, and Measures of Effect in Dental Traumatology

Understanding the etiology of TDI and *associated factors* requires reflecting on three fundamental concepts: (a) dental trauma is a multifactor event; (b) it represents an imbalance between the subject and his/her environment; and (c) it has an evolutionary nature. The etiology of TDI is generally reported in studies as an immediate mechanism by which the trauma occurred, such as a fall from one's own height, fall from a bicycle, or physical aggression. Such characteristics are reported by the patient or caregiver when taking the patient history. *Associated factors* regard the characteristics of the individual, family, or society that contributed to the outcome, which are generally estimated using statistical inference in population-based studies.

With regard to etiology, dental injuries may be the result of an accident or an act of violence. An accident is an unintentional, unavoidable event that causes physical and/or emotional injury either at home or in other social settings, such as the workplace, traffic, and school, or during recreational activities. Violence is an act perpetrated by an individual, group, or nation that causes physical and/or emotional harm. Therefore, trauma produced by violence is non-accidental. Violence perpetrated against children is often associated with neglect or child abuse [5, 21].

The forms of measuring whether a factor is associated with an outcome can be described in different ways. The p-value measures the probability that the difference found (e.g., the difference between exposed and nonexposed individuals with regard to the occurrence of TDI) is due to chance if there are no other differences between groups. It is assumed that if the probability of the difference encountered is small (less than 5% or $p < 0.05$), the factor analyzed is associated with the outcome. The

majority of studies published up to the year 2000 exclusively carried out this type of analysis.

Risk, probability, and chance can be quantified using effect measures. The majority of studies currently describe the number of times the risk, probability, or chance of exhibiting TDI is greater in one group over another. The most employed effect measures are relative risk (RR, for cohort studies), prevalence ratio (PR, for cross-sectional studies), and odds ratio (OR, mainly for case-control studies but also used in observational studies) [10, 22]. The calculation of RR and PR is simple – the frequency of events in the exposed group is divided by the frequency of events in the nonexposed group. For example, for an investigation in which the *prevalence* of TDI in male and female schoolchildren is, respectively, 17% and 10%, the division (17/10) leads to a PR of 1.7, which means that the probability of TDI is 70% higher (or 1.7-fold greater) in the male gender in comparison to the female gender. As this difference may also occur by chance, the 95% confidence interval should also be described in order to determine the statistical significance. The OR is the ratio of the odds in two groups of interest and is more difficult to interpret, especially for clinicians [23]. Moreover, the OR in dental traumatology can strongly overestimate risk, since the *prevalence* of the outcome is usually higher than 20% [24].

When detecting statistical significance between variables that are candidates for *risk factors* and an outcome, clinicians and researchers must first discard the possibility that the association found is spurious (due to chance or bias). Next, the possibility of confounding should be considered. Studies that offer a multivariable analysis – those that describe the statistical significance of different potentially confounding independent variables (performing a "statistical adjustment") – are superior to investigations that exclusively analyze the statistical relationship between two variables.

8.3 Epidemiology in Dental Traumatology

In this item, we describe the frequency of TDI and *associated factors* in the primary and permanent dentitions. For both dentitions, a specific search of the literature was performed to find studies with a sample of at least 300 individuals for the determination of *associated factors* and to enable greater precision in the estimates. The exclusion criteria were studies conducted at hospitals, dental services or dental schools, and investigations that did not adjust the results for possible confounding factors.

8.3.1 Prevalence and Distribution of TDI in Primary Teeth

The majority of epidemiological studies investigating the *prevalence* of TDI and *associated factors* in the primary dentition have been conducted in South America (exclusively in Brazil), with some studies conducted in Asia, a scarcity of data from Europe, Africa, and Central America, and no studies from North America or Oceania. Although considerable variation is found in the frequencies reported, the *prevalence* of TDI in the primary dentition in most studies ranged from 25% to 35%, affecting one quarter to one third of preschoolers. Beginning with the year 2000, most studies employed multivariable analysis and reported effect measures (Table 8.2).

It is generally accepted that the most common injuries in the primary dentition affect the supporting tissues, such as subluxation, lateral luxation, and intrusion [5, 25]. However, it is important to consider that this statement is mainly based on studies conducted at hospitals or other urgent care services, and these data are mainly

Table 8.2 Studies on prevalence of TDI and associated factors in primary dentition identified in studies with multivariable analysis

Author, year	Country	Age (years)	*n*	Prevalence	Associated factors
Hargreaves, 1999 [96]	South Africa	1–5	1466	15.0%	Older age: $p < 0.05$
Granville-Garcia, 2006 [52]	Brazil	1–5	2651	36.8%	Male gender: OR 1.27 (95% CI 1.08–1.15) Older age: OR 2.12 (95% CI 1.49–3.02) Private preschool: OR 1.27 (95% CI 1.08–1.5) Obese/overweight: OR 2.50 (95% CI 1.89–3.30)
Feldens, 2008 [30][a]	Brazil	1	376	15.0%	Higher mother's education: OR 2.61 (95% CI 1.41–4.84) Nonnuclear family: OR 2.28 (95% CI 1.18–4.39)

Table 8.2 (continued)

Author, year	Country	Age (years)	*n*	Prevalence	Associated factors
Jorge, 2009 [39]	Brazil	1–3	519	41.6%	Higher SVI: OR 1.51 (95% CI:1.0–2.2) Lower mother's education: $p = 0.001$
Robson, 2009 [97]	Brazil	0–5	419	39.1%	Male gender: OR 1.62 (95% CI 1.1–2.4) Public preschool: OR 1.95 (95% CI 1.1–3.4) Accentuated overjet: OR 3.72 (95% CI 2.4–5.7) Inadequate lip seal: OR 3.75 (95% CI 1.8–7.7)
Dutra, 2010 [98]	Brazil	1–4	407	47%	Higher number of siblings: OR 2.0 (95% CI 1.1–3.6) Older age: OR 0.6 (95% CI 0.4–0.9)
Feldens 2010 [24]	Brazil	3–5	888	36.4%	Higher mother's education: PR 1.28 (95% CI 1.03–1.60) Accentuated overjet: PR 1.63 (95% CI 1.31–2.03)
Viegas, 2010 [99]	Brazil	5	388	62.1%	Accentuated overjet: OR 2.24 (95% CI 1.11–4.55)
Bonini, 2012 [100]	Brazil	3–4	376	27.7%	Female gender: PR 0.66 (95% CI 0.45–0.96) Accentuated overjet: PR 2.43 (95% CI 1.68–3.53) Open bite: PR 2.15 (95% CI 1.42–3.25)
Norton and O'Connell, 2012 [101]	Ireland	0–6	839	25.6%	Accentuated overjet: OR 2.99 (95% CI 2.0–4.47) Open bite: OR 2.02 (95% CI 1.32–3.08)
Siqueira, 2013 [102]	Brazil	3–5	814	34.6%	Higher family income: PR 1.34 (95% CI 1.05–1.72) Accentuated overjet: PR 1.53 (95% CI 1.21–1.94)
Feldens, 2014 [61][a]	Brazil	4	340	23.7%	Higher family income: RR 1.66 (95% CI 1.08–2.56) Higher breastfeeding duration: RR 0.65 (95% CI 0.43–0.97) Higher frequency of bottle: RR 2.37 (95% CI 1.10–5.11) Higher height for age: RR 1.79 (95% CI 1.03–3.11) Higher number of teeth/12 months: RR 1.74 (95% CI 1.13–2.67)
Antunes, 2015 [103]	Brazil	2–6	606	20.8%	Malocclusion: OR 1.64 (95% CI 1.08–2.49) Accentuated overjet: OR 2.74 (95% CI 1.63–4.61)
Kramer, 2015 [104]	Brazil	0–5	1316	13.3%	Older age: PR 2.24 (95% CI 1.28–3.93) Use of pacifier: PR 1.50 (95% CI 1.08–2.10) Accentuated overjet: PR 2.73 (95% CI 1.77–4.20)
ElKarmi, 2015 [86]	Jordan	4–5	1198	26.4%	Accentuated overjet: OR 1.89 (95% CI 1.36–2.65) Open bite: OR 1.93 (95% CI 1.08–3.47) Inadequate lip seal: OR 2.56 (95% CI 1.58–4.18)

(continued)

Table 8.2 (continued)

Author, year	Country	Age (years)	*n*	Prevalence	Associated factors
Corrêa-Faria, 2015 [94]	Brazil	1–5	301	33.9%	Higher family income: PR 1.52 (95% CI 1.10–2.12) Accentuated overjet: PR 1.53 (95% CI 1.05–2.22) Inadequate lip seal: PR 2.00 (95% CI 1.41–2.84)
Agostini, 2016 [95][b]	Brazil	0–6	1612	21.4%	Older age: PR 2.31 (95% CI 1.66–3.23) Inadequate lip seal: PR 1.51 (95 CI 1.21–1.87)
Tello, 2016 [87][b]	Brazil	1–4	1215	20.1%	Older age: PR 2.57 (95% CI 1.75–3.78) Male gender: PR 1.26 (95% CI 1.01–1.57) Open bite: PR 1.36 (95% CI 1.07–1.72)
Borges, 2017 [74][a]	Brazil	0–3	458	31.0%	Male gender: RR 1.50 (95% CI 1.13–2.00) Smaller head circumference: RR 1.47 (95% CI 1.02–2.11) Overweight/obesity/12 mo: 1.58 (95% CI 1.15–2.17)

[a]Cohort study (others are cross-sectional studies)
[b]Most recent data from different epidemiological surveys performed by same research group in same city

reported by clinicians, who are the health professionals sought under these circumstances. The vast majority of epidemiological studies that investigate factors associated with TDI in children under 6 years of age, however, are performed at preschools or during vaccination campaigns. In such studies, crown fractures are the most frequent type of injury reported, and there is underreporting of injuries to the supporting tissues. Enamel fractures account for the vast majority of crown fractures in preschoolers [26–28]. However, the diagnosis of enamel fracture can be confused or misclassified with another dental condition, such as tooth wear, making it difficult to calibrate examiners, which may also explain the divergence in the frequencies reported in different studies [29].

Regardless of the type of injury and the setting in which the study was conducted, there is a consensus on the most affected region in the primary dentition: the maxillary anterior teeth, especially the central incisors [27, 30].

Another particular aspect of TDI in the primary dentition is the possibility that dental trauma in preschool children, especially those at a younger age, can have negative consequences for the permanent dentition. The main sequelae found in the permanent successors are enamel discoloration, enamel hypoplasia, crown dilaceration, odontoma-like formation, root dilaceration, root duplication, the partial or complete arrest of root formation, sequestration of the tooth germ, and eruption disturbances. This topic is particularly important and is the focus of approximately one fifth of all scientific production on TDI in the primary dentition, especially in the form of case series and cohort studies [31]. Sequelae in the permanent dentition are strongly associated with more severe TDIs in the primary dentition, especially intrusive luxation and avulsion in younger children [32].

Studies that describe the etiology of TDI in the primary dentition emphasize accidents that occur in one's own home, generally due to falls while walking or running, in which the child collides with the floor or a piece of furniture [27, 30].

The *prevalence* rates of TDI and *associated factors* in the primary dentition are described in Table 8.2 and discussed in Item 3.3.

8.3.2 Prevalence and Distribution of TDI in Permanent Teeth

Epidemiological studies investigating the *prevalence* of TDI and *associated factors* in the permanent dentition have predominantly been conducted in South America (exclusively Brazil) and Asia, where several countries have contributed data. Few studies have been conducted in Europe, Africa, and North America, and none have been conducted in Oceania (Table 8.3). The majority

Table 8.3 Studies on prevalence of TDI and associated factors in permanent dentition identified in studies with multivariable analysis

Author, year	Country	Age (years)	*n*	Prevalence	Associated factors
Cortes, 2001 [60]	Brazil	9–14	3702	12.1%	Male gender: OR 1.74 (95% CI 1.41–2.16) Low income: OR 1.43 (95% CI 1.15–1.79) Accentuated overjet: OR 1.37 (95% CI 1.06–1.80) Adequate lip seal: OR 0.48 (95% CI 0.39–0.60)
Marcenes, 2001 [105]	United Kingdom	14	2242	23.7%	Male gender: OR 1.6 (95% CI 1.3–2.0) Overcrowded household: OR 1.1 (95% CI 1.0–1.2) Accentuated overjet: OR 1.4 (95% CI 1.2–1.8)
Marcenes, 2001 [43]	Brazil	12	652	58.6%	Male gender: OR 2.0 (95% CI 1.43–2.74) Higher mother's education: OR 1.60 (95% CI 1.00–2.47)
Traebert, 2004 [106]	Brazil	11–13	2260	10.7%	Male gender: OR 2.17(95% CI 1.55–3.03) Accentuated overjet: OR 2.06 (95% CI 1.40–3.01)
Artun, 2005 [107]	Kuwait	13–14	1583	14.5%	Female gender: OR 0.46 (95% CI 0.34–0.63) Accentuated overjet: OR 1.13 (95% CI 1.05–1.21)
Sgan-Cohen, 2005 [49]	Israel	9–13	1195	29.6%	Female gender: OR 0.69 (95% CI 0.49–0.98) Accentuated overjet: OR 2.51 (95% CI 1.17–5.37) Inadequate lip seal: OR 2.31(95% CI 1.55–3.42)
Moysés, 2006 [62]	Brazil	12	2126	14.4%	Male gender: OR 1.69 (95% CI 1.31–2.19)
Pattussi, 2006 [63]	Brazil	14–15	1302	30.1%	Accentuated overjet: OR 1.82 (95% CI 1.02–3.25)
Soriano, 2007 [73]	Brazil	12	1046	10.5%	Accentuated overjet: OR 3.22 (95% CI 2.13–4.86) Inadequate lip seal: OR 4.29 (95% CI 2.80–6.56)
Ramos-Jorge, 2008 [14][a]	Brazil	11–13	306	7.5% in 2 years	Previous dental trauma: OR 4.85 (95% CI 1,6–14,7)
Naidoo, 2009 [34]	South Africa	11–13	1665	6.4%	Male gender: $p < 0.001$
Bendo, 2010 [57]	Brazil	11–14	1612	17.1%	Male gender: OR 1.12 (95% CI 1.09–1.15) Accentuated overjet: OR 1.15 (95% CI 1.00–1.31) DMFT: OR 1.11 (95% CI 1.06–1.16)
Carvalho, 2010 [108]	Brazil	12–15	1581	37.1%	Male gender: $p = 0.0004$ Lower income: $p = 0.0330$
Livny, 2010 [50]	Israel	11–12	804	17.7%	Male gender: OR 2.0 (95% CI 1.3–3.1) Accentuated overjet: OR 12.7 (95% CI 7.3–22.3) Inadequate lip seal: OR 4.2 (95% CI 1.7–10.4)
Taiwo, 2011 [109]	Nigeria	12	719	15.2%	Male gender: OR 1.6 (95% CI 1.0–2.4)
Bendo, 2012 [110]	Brazil	11–14	1556	14.1%	Male gender: PR 1.41 (95% CI 1.11–1.81) SVI: PR 2.27 (95% CI 1.11–4.61)
Martins, 2012 [92]	Brazil	7–14	590	12.7%	Male gender: OR 1.95 (95% CI 1.17–3.24) Older age: OR 4.9 (95% CI 1.6–14.4) Inadequate lip seal: OR 2.6 (95% CI 1.2–5.4)

(continued)

Table 8.3 (continued)

Author, year	Country	Age (years)	*n*	Prevalence	Associated factors
Patel, 2012 [93]	India	8–13	3708	8.7%	Male gender: $p = 0.029$ Accentuated overjet: OR 3.92 (95% CI 2.72–5.64) Inadequate lip seal: OR 5.41 (95% CI 4.27–6.85)
Damé-Teixeira, 2013 [56]	Brazil	12	1528	34.7%	Male gender: RR 1.41 (95% CI 1.23–1.61) Lower socioeconomic status: RR 1.32 (95% CI 1.07–1.64)
Jorge, 2012 [111]	Brazil	15–19	891	24.7%	Private school: PR 1.11 (95% CI 1.03–1.20) Accentuated overjet: PR 1.17 (95% CI 1.10–1.25)
Schatz, 2013 [112]	Switzerland	6–13	1900	14.3%	Male gender: OR 1.35 (95% CI 1.04–1.78) Accentuated overjet: OR 4.03 (95% CI 2.79–5.81)
Al-Bajjali, 2014 [113]	Jordan	12	1015	16.3%	Male gender: OR 1.42 (95% CI 1.01–2.01) Inadequate lip seal: OR 1.95 (95% CI 1.35–2.81)
Chopra, 2014 [114]	India	12–15	810	10.2%	Overjet: OR 2.44 (95% CI 1.89–3.00) Inadequate lip seal: OR 3.07 (95% CI 2.55–3.59)
De Oliveira, 2014 [81]	Brazil	14–19	701	26.6%	Male gender: PR 1.50 (95% CI 1.17–1.93) Older age: PR 1.61 (95% CI 1.18–2.20) Illicit drug use: PR 1.54 (95% CI 1.06–2.24) Accentuated overjet: PR 1.44 (95% CI 1.13–1.84)
Paiva, 2015 [80]	Brazil	12	588	29.9%	Binge alcohol: OR 1.93 (95% CI 1.21–3.06) Accentuated overjet: OR 3.80 (95% CI 2.24–6.47) Inadequate lip seal: OR 5.59 (95% CI 3.65–8.54)
Frujeri, 2014 [115]	Brazil	12	1389	38.0%	Accentuated overjet: OR 6.43 (95% CI 1.02–30.54) Inadequate lip seal: OR 8.94 (95% CI 5.92–13.51)
Freire, 2014 [116]	Brazil	12	2075	17.3%	Male gender: OR 1.75 (95% CI 1.25–2.47) Lower mother's education: OR 1.97 (95% CI 1.08–3.60)
Bilder, 2015 [117]	Georgia	12–15	823	10.5%	Older age: OR 2.4 (95% CI 1.5–3.9) Rural zone: OR 1.95 (95% CI 1.2–3.2) Accentuated overjet: OR 2.5 (95% CI 1.4–4.5)
Mathur, 2015 [118]	India	12–15	1386	10.9%	Live in deprived areas: OR 3.99 (95% CI 1.86–8.56)
Basha, 2015 [71]	India	6–13	1550	10.5%	Older age: OR 1.97 (95% CI 1.1–3.41) Lower socioeconomic status: OR 2.33 (95% CI 1.05–3.97) Private school: OR 1.23 (95% CI 1.07–2.96) Obesity: OR 2.8 (95% CI 1.84–4.1) Accentuated overjet: OR 3.11 (95% CI 2.06–4.78) Inadequate lip seal: OR 3.01 (95% CI 1.23–4.65)

Table 8.3 (continued)

Author, year	Country	Age (years)	*n*	Prevalence	Associated factors
Paiva, 2015 [80]	Brazil	12	605	34.9%	Accentuated overjet: OR 1.50 (95% CI 1.41–1.61)
Ain, 2016 [90]	India	12	1600	9.3%	Accentuated overjet: $p = 0.00$ Inadequate lip seal: $p = 0.03$ Class II Angle: $p = 0.00$
Ramchandani, 2016 [66]	United Kingdom	15–16	794	17.0%	Problem behavior: OR 1.87 (95% 1.03–3.37)
Baxevanos, 2017 [12]	Grécia	13–16	531	15.8%	Male gender: OR 2.71 (95% CI 1.62–4.54) Schoolmate complaints: OR 1.19 (95% CI 1.04–1.36) Father's support: OR 0.87 (95% CI 0.76–0.99)
Garg, 2017 [119]	India	7–14	3000	10.7%	Male gender: OR 1.29 (95% CI 1.00–1.65) Older age: OR 1.18 (95% CI 1.04–1.34) Inadequate lip seal: OR 1.94 (95% CI 1.16–3.26) Accentuated overjet: OR 7.25 (95% CI 5.03–10.46)
Kramer, 2017 [91]	Brazil	11–14	509	11.6%	Severe malocclusion: OR 1.95 (95% CI 1.01–3.85) Accentuated overjet: OR 1.96 (95% CI 1.14–3.37) Abnormal molar relationship: OR 2.99 (95% CI 2.24–4.32)
Vettore, 2017 [40]	Brazil	12	5027	15.2%	Male gender: OR 1.22 (95% CI 1.06–1.57) Brown ethnicity (vs. white): OR 1.20 (95% CI 1.03–2.40) Overjet: OR 1.40 (95% CI 1.12–1.76)
Silva-Oliveira, 2017 [120]	Brazil	12	588	29.4%	Accentuated overjet: OR 5.61 (95% CI 3.78–8.32) Worst OHRQoL: OR 1.71 (95% CI 1.15–2.54)

SVI social vulnerability index
[a]Cohort study (others are cross-sectional studies)

of these studies were conducted with participants aged 12–15 years, with a mean *prevalence* rate of around 20%, therefore affecting one fifth of adolescents.

The most frequent injuries in the permanent dentition are crown fractures, with a higher proportion than that found in the primary dentition [5]. However, data collected at clinics and hospitals also reveal a substantial proportion of injuries to the supporting tissue, with an emphasis on concussion, subluxation, intrusive luxation, and extrusive luxation [5]. As occurs with the primary dentition, the maxillary anterior teeth, especially the central incisors, are the most affected in the permanent dentition [12, 33].

The etiology of TDI in the permanent dentition varies strongly in accordance with the population type, age group, culture, region in the world, and environment. Such injuries generally occur during falls and sport activities (especially ball sports), traffic accidents, and some forms of violence, such as fights and assault and battery [12, 21, 33, 34].

Variables on different levels have been associated with the occurrence of TDI in the permanent dentition. *Prevalence* rates and *associated factors* are described in Table 8.3 and discussed in Item 3.3.

8.3.3 Factors Associated with TDI in Permanent and Primary Teeth

Like other health conditions, TDI has a multifactor dimension that has been widely discussed, but not yet fully understood. Such aspects are addressed in studies

that identify contextual (group) *risk factors*, such as the social vulnerability of a community, and individual *risk factors* involving different demographic, socioeconomic, behavioral, and biological characteristics [35]. However, it is recognized that such factors act in a differentiated manner on the determination of trauma in different age groups due to their respective particularities. For instance, the effect of parental supervision is greater among very young children (up to 5 years of age) in comparison to adolescents. Similarly, the behavioral characteristics of social groups in adolescence (with an emphasis on violence) seem to play an important role in the occurrence of TDI in the permanent dentition.

The diversity of paradigms that guide studies (ranging from a focus on socioeconomic aspects to exclusively biological aspects) and the difficulties involved in acquiring and interpreting data on causality have limited the understanding of *risk factors* and the interrelations between these factors. Thus, little has been described regarding interactions among individual *risk factors*, especially in the vertical relationships between socioeconomic, behavioral, and biological characteristics [36, 37]. To contribute toward the understanding of the relationships among variables, a hierarchical model of determination has been used on a number of health outcomes [37]. The presupposition is that the variables to be incorporated into the model should be based on a conceptual framework that describes hierarchical relationships among *risk factors*. The variables are grouped on different levels, with socioeconomic and demographic variables occupying a more distal level, behavioral determinants on an intermediate level and biological determinants on a proximal level. This model assumes that each set of variables can affect the outcome, with the direction of influence running from more distal sets to more proximal sets.

However, researchers should not be limited to a particular analytical model. If a hierarchical model is not employed, a discerning interpretation of the findings should be carried out always considering the theoretical background of the outcome in question, which should obviously characterize any analytical model.

Based on the available evidence and considering the aforementioned limitations, a network of *associated factors* involving both contextual and individual variables has been suggested for the occurrence of TDI. These factors are obtained from scientific papers available in the PubMed database using a search of the following keywords in the title or abstract: ("tooth injuries," OR "tooth trauma," OR "dental injuries," OR "traumatized teeth," OR "dental trauma," OR "dentoalveolar trauma," OR "oral trauma") AND (risk OR, associated OR, etiological OR, etiology OR, prevention OR, prevalence OR incidence).

The vast majority of studies exclusively evaluate the relationship between individual variables and the occurrence of TDI, with few investigations assessing the effect of contextual variables. In general, there is consistency in studies regarding the identification of two main *risk factors* of TDI in the permanent dentition: the male gender and accentuated overjet. In the primary dentition, increased overjet is the risk factor repeatedly identified in studies involving different populations. On the other hand, a series of other characteristics, such as obesity and hyperactivity, are identified as *risk factors* in some investigations, but not in others. A description of the different variables evaluated as potential *risk factors* for TDI is offered below. The factors are divided into contextual and individual variables, which are subdivided into socioeconomic, demographic, psychosocial, behavioral, and oral variables. ◘ Figure 8.1 offers a summary of these variables.

8.3.3.1 Contextual Variables

Contextual variables are factors that characterize a country, city, or neighborhood and may be *risk factors* of TDI independently of individual characteristics. While it is recognized that the type of population, culture, and environment can influence the occurrence of different health outcomes [21], few studies have assessed the effect of these factors on the occurrence of TDI. The identification of contextual variables as *risk factors* requires more sophisticated analytical strategies, such as multilevel analysis (in which individual variables are also examined) or georeferencing studies, which offer information regarding the extent to which geographic proximity among cases may be due to environmental factors and not simply a matter of chance.

Moyses et al. (2008) [38] evaluated 327 schoolchildren in the city of Curitiba (Brazil) and found a greater concentration of dental trauma occurrences in areas with substandard living conditions. Evaluating 519 preschoolers between 1 and 3 years of age in the city of Belo Horizonte (Brazil), Jorge et al. (2009) [39] detected a significant association between TDI and the Social Vulnerability Index, which unites information on access to housing, school, income, work, health, and nutrition. Vettore et al. (2017) [40] examined a representative sample of 5027 Brazilian children aged 12 years. The city-level Gini Index was used to measure contextual income inequality in the years 2000 and 2010. The authors found that a reduction in the Gini coefficient in this decade decreased the odds of TDIs even after adjustments for confounding factors and suggested that living in societies with a more unequal distribution of income has a detrimental effect on an individual's health through different mechanisms that are applicable to TDI in children. Although it is not possible to describe consistency

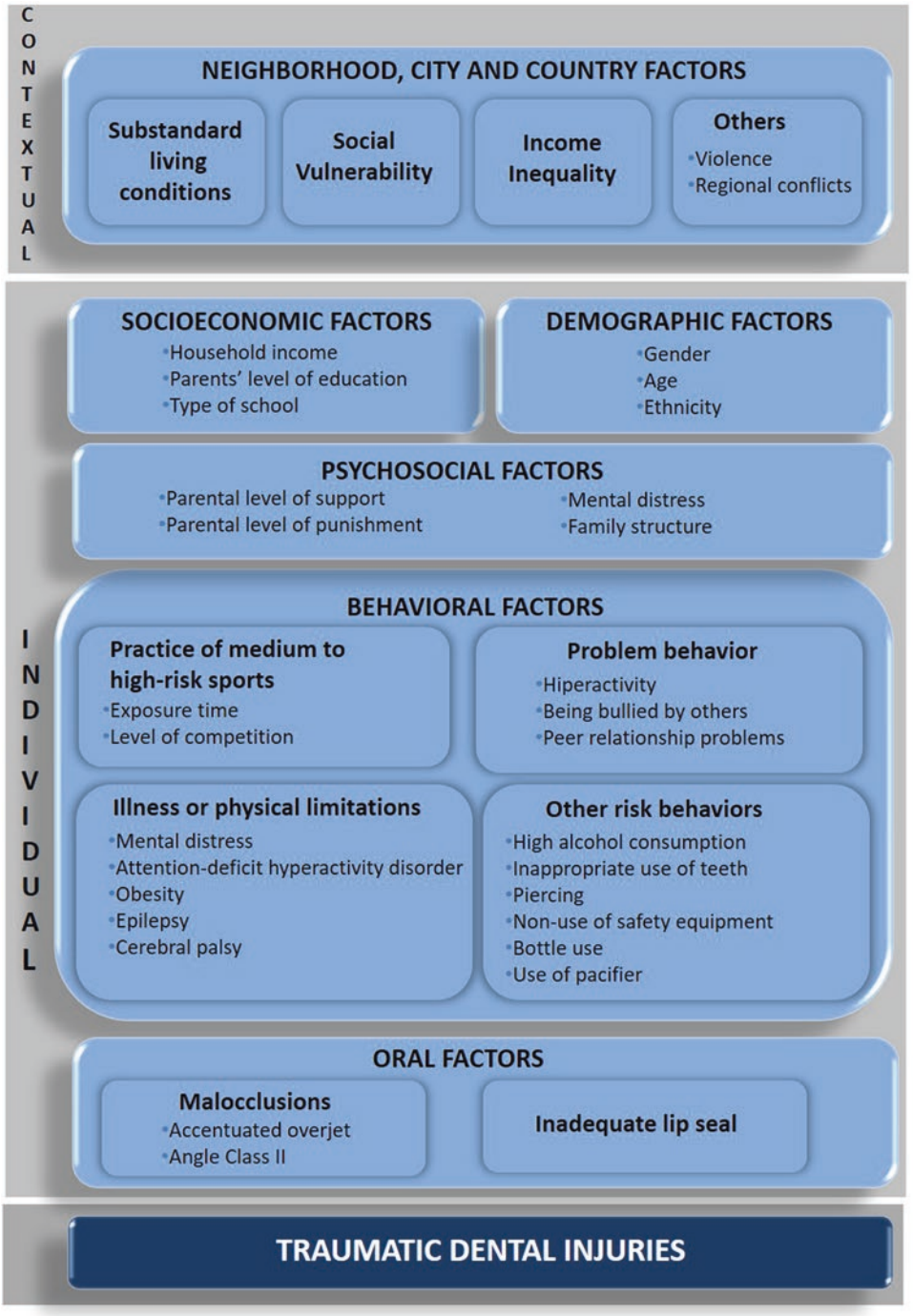


Fig. 8.1 Contextual and individual variables associated with TDI

between these studies, the findings indicate possible regional characteristics that indicate a greater risk of TDI.

The investigation of contextual variables is also an open field for clarifying the network of causality of non-accidental trauma. A number of studies that describe a high *prevalence* rate of TDI report violence to be the main cause. Data from a study by Baghdady et al. (1981) [41] suggest the possible influence of contextual characteristics (high violence index) on the occurrence of TDI in children aged 6–12 years in Sudan and Iraq. Likewise, studies have found that refugees have a high frequency of untreated TDI [42], which demonstrates the effect of a region or country engaged in either internal or external conflict.

Despite the methodological difficulty involved, it seems essential for future investigations to test the influence of contextual variables on the occurrence of TDI.

8.3.3.2 Individual Variables

Individual variables are the characteristics of a child, adolescent, or family that may be associated with the occurrence of TDI. Different studies describe association tests ranging from the report of statistically significant differences (*p*-value) to different effect measures, such as crude measures or measures adjusted for possible confounding factors.

Demographic Factors

Gender

Studies involving schoolchildren and adolescents in different parts of the world have consistently demonstrated that the male gender is a risk factor for TDI [33–35, 43–48]. Traditionally, studies describe a significantly greater occurrence of TDI in males informing a *p*-value, which is generally less than 0.01. In a more informative fashion, a number of studies quantify this difference describing a 50–120% greater frequency of TDI in the male gender [47, 49, 50].

In the primary dentition, most studies have found no significant gender difference [30, 39, 51], whereas some studies report a greater frequency among boys [13, 52]. It is possible that there is a gender difference in some populations of preschoolers regarding TDI. However, a statistically significant difference may not be clinically relevant, that is, it may not be large enough to warrant greater care or orientation given to the parents of male preschoolers. Thus, the characteristics of the male gender that contribute toward the greater occurrence of TDI may be manifested in a more significant manner beginning at school age, with consequences for the permanent dentition.

Age

Studies are generally unanimous in describing that older children have a greater likelihood of exhibiting TDI [28, 52]. However, rather than demonstrating that an older age represents greater risk, this information demonstrates that TDI is a cumulative outcome. Thus, a greater *prevalence* rate among 4-to-5-year-old children in relation to 2-to-3-year-old children does not indicate greater vulnerability. The same is true for the permanent dentition. The analysis of different studies demonstrates that most tooth injuries occur in childhood and adolescence. Indeed, it is estimated that 70–90% of all such injuries sustained in a lifetime occur before the age of 19 years [21]. Longitudinal studies with the determination of outcomes at different ages are the best source of information to clarify what ages are more vulnerable. However, such studies are rare.

Evaluating 1545 preschoolers between 0 and 6 years of age in Canoas (Brazil), Kramer et al. (2003) [28] report *prevalence* rates 0.4%, 9.7%, 18.8%, and 24.8% before 1 year of age and at 1, 2, and 3 years of age, respectively, with the *prevalence* remaining stable thereafter. Oliveira et al. (2007) [51] evaluated 892 children between 5 and 59 months of age in Diadema (Brazil) and found that the *prevalence* of TDI increased from 0.8% among children under 1 year of age to 4.7% among children at 1 year of age and 11% among children at 2 years of age, remaining stable thereafter. Data from the US National Electronic Injury Surveillance System (1990 to 2003) demonstrate an annual occurrence of 22,000 tooth injuries among individuals under the age of 18 years in the country [53], with the 1-to-2-year-old age group accounting for 24.5% of all reported cases of TDI. These findings should be analyzed with caution, since the search for dental services may be associated with greater concern on the part of parents regarding dental trauma in this age group (potential selection bias). Nonetheless, the data draw one's attention to the high occurrence of TDI in the early years of life.

For the permanent dentition, most studies investigate a specific age group, with no consistent identification of the age group at the greatest risk of TDI. Even in studies addressing TDI at different ages (e.g., 11–13 years), the small degree of variation has not allowed detecting statistically significant differences [34]. Glendor et al. (2000) [21] carried out a study involving a cohort of 83 Danish children with TDI experience followed up for a 12-year period and found that the mean age at the first and second episode of TDI was 8.6 and 11.4 years, respectively. Moreover, the risk of exhibiting multiple episodes of TDI was significantly greater (15–30%) among children who experienced their first TDI prior to the age of 11 years.

Socioeconomic Factors

As with other health conditions, individuals with a lower socioeconomic status are generally expected to have a greater risk or likelihood of exhibiting TDI. This situation has been described in both children and adolescents [54–56]. However, some studies have not found a significant association between a low socioeconomic status and TDI [14, 34, 46, 51, 57, 58], and others describe an inverse association [24, 30, 52, 59, 60].

The differences in the findings may be partially explained by the use of different indicators of socioeconomic status (household income, social class, parents' level of education, type of school) as well as the considerable variation in cutoff points. However, it is possible that socioeconomic status exerts an influence in different ways, depending on cultural aspects and issues related to access to safe environments, protective equipment for the avoidance of TDI, and healthcare services in each country. The greater risk of dental injuries among adolescents with a higher socioeconomic status in developing countries may be associated with greater access to bicycles, skateboards, swimming pools, and other risk

conditions in unsafe environments [60, 61]. Moreover, contextual variables (e.g., social cohesion, social capital, and social vulnerability) may exert an influence on the occurrence of TDI [39, 62, 63], which could alter the effect of individual-level variables. Therefore, this important issue needs to be investigated further.

Psychosocial Variables

Psychological and social variables have been investigated in relation to different outcomes, including TDI. Perheentupa et al. (2001) [44] evaluated 31-year-old adults who belonged to a birth cohort and found that mental distress (diagnosed based on the Hopkins Symptom Check List) represented a greater risk for TDI. Likewise, adolescents who have experienced adverse psychosocial environments along their life course seem to be at greater risk for TDI. Nicolau et al. (2003) [35] evaluated 652 13-year olds and found that adolescents from nonnuclear families and those reporting high levels of paternal punishment had a greater chance of exhibiting TDI, even after adjusting for possible confounding variables. Baxevanos et al. (2017) [12] investigated associations between TDI and psychosocial variables in 531 adolescents aged 13–16 years and found that those with high parental support and those whose mothers had a strong sense of coherence had lower TDI experience.

While it is difficult to establish the exact mechanism by which these adolescents are more exposed, it is possible that such characteristics are associated with behaviors that offer a greater risk of accidental or non-accidental injuries.

A greater *incidence* of TDI in the early years of life has also been reported in children who live in nonnuclear families (i.e., the child does not live with both parents) [30]. In such cases, it is possible that less parental supervision is the mechanism involved.

Behavioral Variables

A number of studies have related the occurrence of TDI with particular behavioral characteristics in children and adolescents [21]. Ramos-Jorge et al. (2008) [14] compared a cohort of adolescents with previous TDI experience to those with no history of TDI and found that the *incidence* of trauma in 2 years was much higher in the former group (11.9% versus 2.7%). The adjusted chance of TDI was nearly fivefold greater among those with a previous TDI. Likewise, children with previous trauma in the primary dentition are prone to trauma in the permanent dentition [64]. These data suggest individual behavioral factors that represent a high risk of TDI.

Such behavioral characteristics may simply constitute the practice of a sport considered to be of high risk (e.g., skating), or small alterations from the pattern considered "healthy" (such as hyperactivity) may be associated with other behaviors identified as a risk for other conditions (such as obesity) or may stem from a systemic disease (such as epilepsy). The plausibility of the relationship between these characteristics and TDI resides in the fact that such behaviors expose a child or adolescent to more falls, collisions, or violence. A description of the main behavioral characteristics suggested associated with TDI is offered below.

Practice of Sports

A number of studies report that the practice of some sports is a risk for the occurrence of TDI. The *Federation Dentaire International* categorizes sports into two categories of risk for TDI [21, 65]:

(a) High-risk sports: Team sports in which rough contact between the players is allowed or in which a ball, puck, or stick is used but also some individual sports for which good balance is required. These are characteristics of American football, hockey, ice hockey, martial arts, rugby, skateboarding, and mountain biking.
(b) Medium-risk sports: Team sports in which rough contact between the players is not allowed, but there is still a risk of contact or falls (e.g., basketball, soccer, team handball, diving, squash, gymnastics, parachuting, and water polo).

The risk of TDI in the practice of sports also depends on the level of competition (amateur or professional) and exposure time [21]. Considerable variation in the relationship between sports and TDI is found across countries, as the practice of sports depends on historical and cultural issues in each community. Nonetheless, knowledge on the risk of each type of sport is fundamental to the establishment of specific protection measures.

Problem Behavior

Problem behavior is socially defined as a problem or undesired action in light of the norms of society, and its *incidence* usually elicits some kind of social response [59], such as hostile aggression against peers, vandalism, and hyperactivity.

While the association between problem behavior and TDI is plausible, few studies have investigated this relationship. The greatest difficulty in this regard is how to define "problem behavior" in a study. Odoi et al. (2002) [59] evaluated 170 children aged 7–15 years in a case-control study using the Strengths and Difficulties Questionnaire (SDQ) to identify problem behavior. The authors found that the adjusted chance of having a TDI was 2.4-fold greater among children with peer relationship problems, such as being picked on or bullied by other children. Moreover, exhibiting pro-social behavior, such as often volunteering to help parents, teachers,

and other children, had a protective effect (OR = 0.24). No significant associations were found between TDI and other types of problem behavior, such as hyperactivity or emotional symptoms. Moreover, children who had conduct problems, such as fighting or bullying other children, were not more likely to exhibit TDI than those who did not have such problems, probably because they were the aggressors.

Recently, Ramchandani et al. (2016) [66] investigated 794 adolescents from London and found that participants with problem behavior assessed using the SDQ, especially those with peer problems, were more likely to have TDI. Evaluating a representative sample of 5913 children aged 4–15 years in the Health Survey for England, Laloo (2003) [67] found that hyperactive children had a greater risk of injuries affecting the face and/or teeth in comparison to children without this disorder. The difficulty in defining behavioral problems, such as hyperactivity, in epidemiological studies may at least partially explain the difference in the results of this study and other investigations that found no greater risk of TDI [59] or other types of injuries [68] in children with hyperactivity.

Considering the plausibility of the association, the use of validated tools to investigate the role of problem behavior is a promising field in the etiological study of TDI and may serve as the basis for prevention strategies.

Illness or Physical Limitations

Children and adolescents with attention deficit hyperactivity disorder (ADHD) have been described as being at greater risk for the occurrence of TDI [69, 70]. The plausibility of this association resides in the fact that violence, which is a significant risk factor for TDI, is more likely to be observed in conduct disorder, which is a common comorbidity of ADHD.

A number of studies have suggested that obesity is a risk factor for TDI in adults [44], schoolchildren [35, 71–73], and preschoolers [52, 74]. However, other studies have not found such an association [45, 56]. Obesity was determined in different manners in the studies cited, such as body mass index or the criteria of the US National Center for Health Statistics, which may at least partially explain the differences. It is plausible that anthropometric variables, especially those potentially associated with postural balance, such as obesity, may be associated with the occurrence of accidental trauma [74].

Other conditions that involve physical limitations have been described as associated with TDI in children and adolescents, such as epilepsy [75], cerebral palsy [76, 77], learning difficulties [78], and hearing or visual impairment [79]. A lack of motor coordination, crowded conditions at institutions, and a lower self-defense mechanism with regard to falls and collisions are possible explanations for the findings reported [21].

Other Risk Behaviors

Other risk behaviors for the occurrence of TDI have been identified, such as high alcohol consumption [80]; the use of illicit drugs [81]; inappropriate use of teeth as a tool to open hair clips, fix electronic equipment, cut or hold objects, or open bottles of soda or beer [33]; piercing the tongue and lips, which may lead to fractured teeth, pulp damage, or tooth abrasion [82]; and the nonuse of specific protection equipment, such as a seatbelt [83] or bicycle helmets [84]. Although these associations need to be replicated in different populations, they are plausible and may contribute to collective TDI prevention strategies.

The apparently conflicting results in studies that investigate the role of different behaviors in the occurrence of TDI should be interpreted with caution. In studies that have not found an association, it is possible that the environment plays a more important role than human behavior; for instance, a hyperactive child can express his or her hyperactivity with less risk in a safe environment [21]. The determination that different behavioral factors, especially those related to general health alterations, are associated with TDI indicates that the clarification of these issues should be the focus of interdisciplinary studies. The knowledge generated in such studies will have implications in different fields as well as in the development and implementation of prevention strategies.

Oral Factors

Accentuated overjet stands out among the few variables consistently demonstrated as *risk factors* for the occurrence of TDI [85]. To some extent associated with overjet, a number of studies have reported that Angle Class II and inadequate lip seal are also *risk factors*, as children and adolescents with this condition are more exposed to fractures and dislocations in cases of falls and collisions. Regarding the primary dentition, some studies have reported that children with anterior open bite are at greater risk of TDI [86, 87], but it is plausible that this association occurs due to a greater proportion of overjet and inadequate lip seal in these patients.

Increased Overjet

Increased overjet is the most commonly identified risk factor for TDI in both the primary [24, 51] and permanent [49, 50, 57, 73, 80, 85] dentition. In the permanent dentition, there is considerable variation in the quantification of this association among studies, which may be explained by the different cutoff points employed (>2 mm to >6 mm).

Most studies report an important increase in the magnitude of the risk of TDI in children with accentuated overjet (generally twofold greater), even after the multivariable analysis [49, 88]. Some studies, however,

report an even greater effect, with the odds ranging from 5 [89] to 12 times greater [50] in children with accentuated overjet. The effect size also seems to be greater with a greater amount of overjet [88]. In the primary dentition, the increased likelihood of TDI in children with accentuated overjet ranges from 65% [24] to 110% [51].

A meta-analysis was conducted to measure the real effect of overjet considering discrepancies in the criteria used for the cutoff point for accentuated overjet and the need to provide reliable risk estimates on the global level [85]. Fifty-four primary studies were included, totaling more than 10,000 patients with TDI. The pooled estimates resulted in 2.31 (95% CI: 1.01–5.27) for an overjet threshold of 3–4 mm in the primary dentition as well as 2.01 (95% CI: 1.39–2.91) and 2.24 (95% CI: 1.56–3.21) for an overjet threshold 3–4 mm and 6.1 ± 1 mm, respectively, in the permanent dentition. The fraction of global TDI attributable to accentuated overjet was 21.8%. These findings suggest that preventive measures against TDI should be implemented in patients with accentuated overjet.

Angle Class II

Studies involving adolescents in India and Brazil report a greater occurrence of TDI in the presence of Angle Class II and a distal step molar relationship, respectively [90, 91]. The association between TDI and an abnormal relationship remained even after controlling for overjet, demonstrating an independent effect of this malocclusion [91]. The plausibility of such associations resides in the increase in the level of exposure to traumatic injuries in adolescents with maxillary protrusion or protruded maxillary anterior teeth. It is also possible that such conditions determine insufficient lip seal [91]. Increased overjet and Angle Class II are modifiable conditions and should therefore be the focus of interventions for the prevention of TDI.

Inadequate Lip Seal

A large portion of children who seek treatment following trauma to the face have a lip injury and do not necessarily exhibit a detectable injury in the dental tissues. Thus, it is plausible that inadequate lip protection is another risk factor for the occurrence of dental fractures and displacement. On the other hand, it is undeniable that accentuated overjet and inadequate lip protection are associated, and it is difficult to separate the effect of these two conditions. The debate seems to regard the extent to which overjet and insufficient lip coverage (either combined or separately) increase the risk of TDI [21].

In general, studies addressing this issue have detected an association between inadequate lip protection and TDI in the permanent [49, 50, 60, 92, 93] and primary [86, 94, 95] dentition even after adjustment for confounding factors. Performing a separate quantification of the effect of accentuated overjet and inadequate lip protection has important clinical implications.

Points of Emphasis

The most consistently described factors associated with TDI in studies are:

- Male gender
- Accentuated overjet
- Inadequate lip seal

Moreover, important psychosocial and behavioral factors have been reported.

8.4 Impact of TDI

Traumatic dental injuries can cause esthetic, psychological, social, and functional problems, with a high cost for families and society not only at the time of the accident but also during later treatment [5, 21]. In recent decades, studies have estimated the impact of different oral problems on *oral health-related quality of life* (OHRQoL), which is defined as a multidimensional concept regarding subjective evaluations of oral health, functional well-being, expectations/satisfaction with care, and sense of self [121]. The measurement of OHRQoL together with clinical indicators provides a more comprehensive assessment of a patient's oral health [122].

Studies that have estimated the impact on TDI on OHRQoL are described below and generally performed a cross-sectional evaluation of OHRQoL between participants with and without TDI experience. Few studies have prospectively investigated the impact of treatment for TDI on OHRQoL.

8.4.1 Impact of TDI in Primary Teeth on OHRQoL

Studies investigating the impact on TDI in the primary dentition on OHRQoL have been conducted in Brazil with a cross-sectional design and nearly all employed the Early Childhood Oral Health Impact Scale (ECOHIS). The outcome was impact determined by the overall score and scores on the child impact section (CIS) and family impact section (FIS) as well as the symptoms and functional, psychological, and social domains. Some studies dichotomized scores as "no impact" or "any impact." Table 8.4 shows that the findings of individual studies are not consistent, as some describe that TDI had significant impact on OHRQoL, whereas others describe no impact. Although most studies used the occurrence of any type of TDI as the outcome, some evaluated the

Table 8.4 Studies that investigated impact of TDI in primary teeth on OHRQoL

Author, year	Country	Age (years)	*n*	OHRQoL instrument	Results
Aldrigui, 2011 [124]	Brazil	2–5	260	ECOHIS	Impact on total ECOHIS[a]
Viegas, 2012 [125]	Brazil	5–6	388	ECOHIS	X
Siqueira, 2013 [102]	Brazil	3–5	814	ECOHIS	X
Kramer, 2013 [126]	Brazil	2–5	1036	ECOHIS	Impact on total ECOHIS[a]
Gomes, 2014 [127]	Brazil	3–5	843	ECOHIS	Impact on CIS[a], not on FIS
Guedes, 2014 [128]	Brazil	1–5	478	ECOHIS	Impact on total ECOHIS[a]
Viegas, 2014 [129]	Brazil	5–6	1632	ECOHIS	X
Abanto, 2015 [130]	Brazil	1–4	1215	ECOHIS	X
Firmino, 2015 [131][b]	Brazil	3–5	415	ECOHIS	Impact on CIS[a]
Vieira-Andrade, 2015 [132][b]	Brazil	3–5	335	ECOHIS	X
Feldens, 2016 [29]	Brazil	1–5	1488	ECOHIS	Impact on total ECOHIS[a]
Ramos-Jorge, 2017 [123]	Brazil	3–5	459	ECOHIS	Impact on total ECOHIS[a]
Gomes, 2018 [133]	Brazil	5	769	SOHO-5	Impact on total SOHO-5[a]

X not associated, *SVI* social vulnerability index, *SOHO-5* scale of oral health outcomes for 5-year-old children
[a]Multivariable analysis
[b]Case-control study (others are cross-sectional studies)

effect of specific injuries or conditions. Discoloration of the crown was found to exert a negative impact on OHRQoL [123], whereas enamel fracture had no impact on the OHRQoL of preschool children [29].

A recent systematic review [13] united the findings of 10 studies comprising a total population of 7461 preschool children, and 9 studies were included in the meta-analysis. TDI caused a negative impact on OHRQoL based on the overall ECOHIS score (OR = 1.24; 95% CI: 1.08–1.43) and CIS score (OR = 1.23; 95% CI: 1.07–1.41), but not the FIS score (OR = 1.09; 95% CI: 0.90–1.32). These results demonstrate the need for prevention strategies and immediate treatment for TDI in early childhood.

8.4.2 Impact of TDI in Permanent Teeth on OHRQoL

Studies investigating the impact of TDI in the permanent dentition on OHRQoL have been conducted in different communities (predominantly in Brazil) using a cross-sectional design and employing the Child Perceptions Questionnaire ($CPQ_{11–14}$), the children's version of the Oral Impacts on Daily Performance (Child-OIDP), and the Oral Health Impacts Profile questionnaire (OHIP-14). Some studies estimated the effect of untreated *traumatic dental injuries* separately. As outcomes, mean scores were generally compared between individuals with and without a history of TDI, and the impact on different domains was investigated. Table 8.5 shows that the findings of the individual studies are not consistent.

Zaror et al. (2017) [122] united the findings of 6 studies on the permanent dentition in a systematic review comprising a total population of 3332 schoolchildren. All studies were included in the meta-analysis. The results demonstrated that TDI exerted a negative impact on OHRQoL (OR = 1.31; 95% CI: 1.04–1.66) and the social domain was the most affected in schoolchildren [122]. Although the lack of consistency in the results of individual studies may be related to the small sample size, one must bear in mind the wide variation in the severity of TDI. It is possible that the high *prevalence* of milder types of TDI, such as enamel fractures, can diminish or even nullify the impact of the set of TDIs on OHRQoL, as demonstrated for the primary dentition [29].

The treatment of TDI can contribute to OHRQoL, as suggested by the majority of cross-sectional studies that compare quality of life scores between adolescents with treated and untreated TDI [57, 134] as well as studies that longitudinally compare scores before and after treatment [135].

Table 8.5 Studies that investigated impact of TDI in permanent teeth on OHRQoL

Author, year	Country	Age (years)	*n*	OHRQoL instrument	Results
Locker, 2007 [136]	Canada	11–14	370	CPQ_{11-14}	Impact on total CPQ[a]
Bendo, 2010 [137]	Brazil	11–14	1612	CPQ_{11-14}	Impact on social well-being[a]
Piovesan, 2011 [138]	Brazil	12	792	CPQ_{11-14}	X
Paula, 2012 [139]	Brazil	12	515	CPQ_{11-14}	X
Traebert, 2012 [140]	Brazil	11–14	403	CPQ_{11-14}	Impact on total CPQ[a]
Damé-Teixeira, 2013 [141]	Brazil	12	1528	CPQ_{11-14}	Impact on functional limitations[a]
Bendo, 2014 [142][b]	Brazil	11–14	1215	CPQ_{11-14}	Impact on total CPQ[a]
Ramos-Jorge, 2014 [134]	Brazil	11–14	668	Child-OIDP	Impact on total child-OIDP[a]
Pulache, 2016 [143]	Peru	11–14	473	CPQ_{11-14}	Impact on social well-being[a]
Bomfim, 2017 [144]	Brazil	12	7240	OHRQoL[c]	Impact on feelings of shame, dissatisfaction with teeth, difficulty to eat and study[a]
El-Kalla, 2017 [145]	Egypt	11–14	11,700	CPQ_{11-14}	Impact on total CPQ
Martins, 2017 [146]	Brazil	8–10	546	CPQ_{8-10}	X
Martins, 2018 [147]	Brazil	8–10	1204	CPQ_{8-10}	X
Keles, 2018 [148]	Turkey	14–18	585	OHIP-14	Impact on total OHIP-14
Silva-Oliveira, 2018 [120]	Brazil	12	588	CPQ_{11-14}	Impact on total CPQ[a]
Soares, 2018 [149]	Brazil	8–10	1589	CPQ_{8-10}	Impact on total CPQ[a]

X not associated
[a]Multivariable analysis
[b]Case-control study (others are cross-sectional studies)
[c]OHRQoL measured with questions regarding satisfaction with teeth, difficulty to eat, feeling shame, and difficulty to study

8.5 Interventions in Dental Traumatology

The World Health Organization proposes actions on different levels: avoiding the occurrence of disease (primary prevention); early diagnosis and prompt care before greater complications occur (secondary prevention); and the reduction of adverse effects and functional rehabilitation (tertiary prevention) [150]. These levels of prevention represent possible opportunities for the action of health professionals regarding the approach to TDI, especially considering the high *prevalence* and impact of this condition.

Oral health professionals are the primary individuals responsible for planning and organizing prevention strategies on different levels as well as educating other medical and nonmedical professionals [2]. Moreover, teachers play a fundamental role in first aid for TDI and can influence the prognosis, as a substantial number of accidents or acts of violence occur in the school setting and require immediate care. However, knowledge on the part of teachers regarding first aid after a tooth injury is insufficient [151]. Furthermore, some school managers have a very fragmented vision, in which teachers' education does not require or even should not include knowledge regarding health and disease [151]. These facts clearly indicate a potential focus of intervention.

Recently, applications for smartphones have been tested for the remote diagnosis of TDI and as an aid in the emergency management of traumatized teeth [152–154]. The results have demonstrated that the remote diagnosis was in good agreement with the diagnosis given in person [152, 153]. Moreover, the TDI app alone was effective in providing accessible knowledge to guide laypersons in managing a tooth avulsion [152]. Dental trauma apps may also serve as a gateway for raising awareness with regard to TDI [155].

8.5.1 Primary Prevention in Dental Traumatology

Primary prevention involves health promotion (environmental and behavioral) actions as well as specific protection strategies, such as the promotion of healthy environments in the home, neighborhood, city, and country with the potential to avoid accidents and violence. In the broad sense, health professionals can contribute to collective actions, such as (a) participation in social accident prevention instruments; (b) support, planning, regulation, and implementation of healthy environments in private and public collective environments, such as schools, community centers, and parks; and (c) the promotion of healthy, nonviolent behavior.

Actions with the potential to prevent TDI can also be directed at the nuclear family, such as (a) sensitization and awareness of caregivers about child supervision; (b) formulation of proposals for physical alterations of the home space; and (c) the institution of specific protection measures, when indicated.

TDI protection measures may be passive or active. In passive protection, the possible victim is protected independently of his/her actions through the use of adequate flooring or padding applied to furniture that offers risk. The installation and conservation of playground equipment seems to be a special measure for the prevention of tooth injuries in childhood. Active protection requires actions in recognized situations of risk, such as the use of a mouthguard or specially designed car seats, which are simple, effective measured for preventing accidents.

On the other hand, specific *risk factors* identified in studies should be the focus of preventive actions. As accentuated overjet is the most consistently recognized risk factor for the occurrence of TDI in childhood [31], there is a need for specific orientation regarding the prevention, control, and reduction of this malocclusion, such as counseling with regard to the use of a pacifier, bottle feeding, and thumb sucking.

However, the primary prevention measures suggested are based on the results of observational studies and the understanding of *risk factors*. The effectiveness of such measures has not been demonstrated in intervention studies.

8.5.2 Secondary and Tertiary Prevention in Dental Traumatology

The immediate treatment of TDI is not dissociable from the continuous treatment that TDI in both dentitions requires, often accompanied by functional rehabilitation. Therefore, secondary and tertiary preventions are necessary in the majority of tooth injuries. Once TDI has occurred, early diagnosis and prompt treatment are essential. Besides the scarcity of randomized clinical trials, the broad variety of tooth injuries also constitutes a challenge to the establishment of protocols. Such injuries are divided into 8 fractures and 6 luxation entities, and combinations constitute nearly 50 types of injuries and distinct healing scenarios [6].

Oral health services should be organized in such a way as to meet the needs of spontaneous demands for care and urgent cases. The basis of clinical conduct and counseling in cases of TDI should be clinical protocols based on the best available scientific evidence. This presupposition is essential to an effective universal healthcare system, with an indirect influence on the increase in cure indices and improvements in the quality of life of the patients.

Table 8.6 summarizes the treatment and prognosis of different types of TDI in the primary and permanent

Table 8.6 Treatment and prognosis according to each traumatic dental injury in primary (pt) and permanent teeth (PT)

Type of TDI	Treatment	Prognosis	References
Injuries to dental tissues			
Enamel fracture	pt – Monitoring or contouring	Favorable	Bourguignon 2020 [25], Day 2020 [157]
	PT – Monitoring or contouring or restoration		
Enamel-dentine fracture	pt – Monitoring or restoration	Favorable	Bourguignon 2020 [25], Day 2020 [157]
	PT – Restoration		
Enamel-dentine-pulp fracture	pt/PT: Pulp treatment + restoration	pt – Questionable	Bourguignon 2020 [25], Day 2020 [157], Wang 2017 [158]
		PT – Favorable	
Crown-root fracture	pt – Extraction	pt – Unfavorable	Bourguignon 2020 [25], Day 2020 [157]
	PT – Multidisciplinary	PT – Questionable	

Table 8.6 (continued)

Type of TDI	Treatment	Prognosis	References
Root fracture	pt – Monitoring	Questionable	Bourguignon 2020 [25], Day 2020 [157]
	PT – Repositioning + stabilization		
Injuries to supporting tissues			
Concussion	pt/PT: Monitoring	Favorable	Bourguignon 2020 [25], Day 2020 [157], Lauridsen 2017a [159]
Subluxation	pt/PT: Monitoring	Favorable	Fried 1996 [160], Bourguignon 2020 [25], Day 2020 [157], Lauridsen 2017a [159]
Lateral and extrusive luxation	pt – Monitoring or repositioning Repositioning + stabilization	Questionable	Cunha 2007 [161], Bourguignon 2020 [25], Day 2020 [157], Cho 2017 [162], Lauridsen 2017b [163]
	PT – Repositioning + stabilization		
Intrusion	DT – Monitoring	pt – Favorable	Spinas 2006 [164], Colak 2009 [165], Bourguignon 2020 [25], Day 2020 [157], Lauridsen 2017c [166]
	PT – Monitoring or repositioning Repositioning + stabilization	PT – Questionable	
Avulsion	pt – Replantation not recommended	Unfavorable	Hinckfuss and Messer 2009a [167], Hinckfuss and Messer 2009b [168], Hinckfuss and Messer 2009c [169], Petrovic 2010 [170], Fouad 2020 [171]
	PT – Replantation		

dentitions based on a systematic search of the best available evidence. The guidelines of the International Association of Dental Traumatology (IADT) were also considered, as these recommendations were defined based on systematic searches of the literature, including cohort studies that followed up treated patients. Bücher et al. (2013) [156] investigated whether the IADT guidelines result in lower complication rates using survival analysis on 361 dental injuries in 291 patients. The authors found that adherence to the IADT guidelines for treatment of dental trauma may lead to more favorable outcomes. The suggested conducts have a moderate degree of recommendation, indicating a moderate level of evidence, generally based on cohort studies or the IADT guidelines. Randomized clinical trials in the field of TDI are scarce due to the limitations discussed in this chapter and are restricted to the treatment of tooth avulsion.

8.6 Conclusions

The World Health Organization recommends the following strategies for improving the oral health of populations: (1) a reduction in the burden of oral disease, especially in needy communities; (2) the promotion of healthy lifestyles and reduction in *risk factors* that stem from environmental, economic, social, and behavioral causes; (3) the development of equitable healthcare systems that improve oral health outcomes and meet the demands of the population; and (4) the integration of oral health in collective health programs [172, 173].

Traumatic dental injuries (TDI) are among the most prevalent oral health problems and have physical, emotional, and economic consequences to the affected individual and his/her family as well as implications for society as a whole [124, 140]. Developing programs aimed at preventing and controlling TDI is a challenge to healthcare professionals and administrators. Planning and executing intervention studies of good methodological quality based on preventive actions and treatment constitute a challenge for researchers.

Nonetheless, health professionals should break the bonds of inertia and develop strategies that can contribute to preventing and lowering the rate of TDI on the population, institutional, and familial levels. Health promotion is a sociopolitical process that proposes the adoption of healthy habits and lifestyles on both the individual and collective levels as well as the creation of safe environments. Besides educational actions, it is also important to map situations of risk in the community and participate in social control and accident prevention measures. The implementation of health promotion programs and strategies necessarily involves an understanding of the factors associated with the imbalance in the health-illness process. However, TDI has a complex, multifactor network of causality, and few significant *risk factors* have been consistently confirmed thus far. The available evidence demonstrates that TDI mainly affects young males (adolescents) and accentuated over-

jet is the main oral characteristic highlighted as a significant risk factor. Furthermore, a history of TDI has also been found to be a predisposing factor. Several social, environmental, and behavior factors have been associated with TDI but need to be clarified in future investigations.

The evidence clearly indicates that the approach to this issue should involve interdisciplinary actions and the investigation of *risk factors* common to other health conditions. There is a growing consensus that oral health measures should be incorporated into general health programs. In consonance with the general strategy of the World Health Organization, the incorporation of such measures into general health programs will potentially improve health and reduce inequalities in high-risk communities.

8

References

1. Andreasen JO, Lauridsen E, Andreasen FM. Contradictions in the treatment of traumatic dental injuries and ways to proceed in dental trauma research. Dent Traumatol. 2010;26(1):16–22.
2. Levin L, Zadik Y. Education on and prevention of dental trauma: it's time to act! Dent Traumatol. 2012;28(1):49–54.
3. Feldens CA, Kramer PF, Feldens EG. Exploring the profile of articles on traumatic dental injuries in pediatric dental journals. Dent Traumatol. 2013;29(3):172–7.
4. Feliciano KMPDC, Caldas ADF. A systematic review of the diagnostic classifications of traumatic dental injuries. Dent Traumatol. 2006;22(2):71–6.
5. Andreasen JO, Andreasen FM, Andersson L. Textbook and color atlas of traumatic injuries to the teeth. 4th ed. Oxford: Wiley-Blackwell; 2007.
6. International Association of Dental Traumatology. Dental trauma guide. Available at https://dentaltraumaguide.org/
7. Sharif MO, Tejani-Sharif A, Kenny K, Day PF. A systematic review of outcome measures used in clinical trials of treatment interventions following traumatic dental injuries. Dent Traumatol. 2015;31(6):422–8.
8. Kenny KP, Day PF, Sharif MO, et al. What are the important outcomes in traumatic dental injuries? An international approach to the development of a core outcome set. Dent Traumatol. 2018;34(1):4–11
9. Andersson L, Andreasen JO. Important considerations for designing and reporting epidemiologic and clinical studies in dental traumatology. Dent Traumatol. 2011;27(4):269–74.
10. Rothman KJ, Greenland S, Lasch TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
11. Bastone EB, Freer TJ, McNamara JR. Epidemiology of dental trauma: a review of the literature. Aust Dent J. 2000;45(1):2–9.
12. Baxevanos K, Topitsoglou V, Menexes G, Kalfas S. Psychosocial factors and traumatic dental injuries among adolescents. Community Dent Oral Epidemiol. 2017;45(5):449–57.
13. Borges TS, Chaffee BW, Kramer PF, Feldens EG, Vítolo MR, Feldens CA. Relationship between overweight/obesity in the first year of age and traumatic dental injuries in early childhood: findings from a birth cohort study. Dent Traumatol. 2017;33(6):465–71.
14. Ramos-Jorge ML, Peres MA, Traebert J, et al. Incidence of dental trauma among adolescents: a prospective cohort study. Dent Traumatol. 2008;24(2):159–63.
15. Hermann NV, Lauridsen E, Ahrensburg SS, Gerds TA, Andreasen JO. Periodontal healing complications following extrusive and lateral luxation in the permanent dentition: a longitudinal cohort study. Dent Traumatol. 2012;28(5):394–402.
16. Andreasen JO, Ravn JJ. The effect of traumatic injuries to primary teeth on their permanent successors: II. A clinical and radiographic follow-up study of 213 teeth. Eur J Oral Sci. 1971;79(3):284–94.
17. Holan G, Diana RD. Sequelae and prognosis of intruded primary incisors: a retrospective study. Pediatr Dent. 1999;21(4):242–7.
18. Ramos-Jorge ML, Ramos-Jorge J, Mota-Veloso I, Oliva KJ, Zarzar PM, Marques LS. Parents' recognition of dental trauma in their children. Dent Traumatol. 2013;29(4):266–71.
19. Costa VPP, Amaral CC, Goettems ML, Pinheiro RT, Demarco FF. Maternal perception of the occurrence of traumatic dental injuries in children: a cohort study of south Brazil. Int Dent J. 2016;66(3):163–8.
20. Andreasen JQ, Ravn JJ. Epidemiology of traumatic dental injuries to primary and permanent teeth in a Danish population sample. Int J Oral Surg. 1972;1(5):235–9.
21. Glendor U. Aetiology and risk factors related to traumatic dental injuries – a review of the literature. Dent Traumatol. 2009;25(1):19–31.
22. Fletcher RH, Fletcher SW. Clinical epidemiology: the essentials. Baltimore: Lippincott Williams & Wilkins; 2005.
23. Kirkwood BR, Sterne JAC. Essential medical statistics. 2nd ed. Oxford: Blackwell Science; 2003.
24. Feldens CA, Kramer PF, Ferreira SH, Spiguel MH, Marquezan M. Exploring factors associated with traumatic dental injuries in preschool children: a Poisson regression analysis. Dent Traumatol. 2010;26(2):143–8.
25. Bourguignon, C, Cohenca, N, Lauridsen, E, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 1. Fractures and luxations. Dent Traumatol. 2020; 36: 314– 330.
26. Ferguson FS, Ripa LW. Prevalence and type of traumatic injuries to the anterior teeth of preschool children. J Pedod. 1979;3(1):3–8.
27. Hasan AA, Qudeimat MA, Andersson L. Prevalence of traumatic dental injuries in preschool children in Kuwait - a screening study. Dent Traumatol. 2010;26(4):346–50.
28. Kramer PF, Zembruski C, Ferreira SH, Feldens CA. Traumatic dental injuries in Brazilian preschool children. Dent Traumatol. 2003;19(6):299–303.
29. Feldens CA, Day P, Borges TS, Feldens EG, Kramer PF. Enamel fracture in the primary dentition has no impact on children's quality of life: implications for clinicians and researchers. Dent Traumatol. 2016;32(2):103–9.
30. Feldens CA, Kramer PF, Vidal SG, Faraco IM Jr, Vítolo MR. Traumatic dental injuries in the first year of life and associated factors in Brazilian infants. J Dent Child. 2008;75(1):7–13.
31. Kramer PF, Onetto J, Flores MT, Borges TS, Feldens CA. Traumatic dental injuries in the primary dentition: a 15-year bibliometric analysis of dental traumatology. Dent Traumatol. 2016;32(5):341–6.
32. Lenzi MM, Alexandria AK, Ferreira DMTP, Maia LC. Does trauma in the primary dentition cause sequelae in permanent successors? A systematic review. Dent Traumatol. 2015;31(2):79–88.
33. Malikaew P, Watt RG, Sheiham A. Prevalence and factors associated with traumatic dental injuries (TDI) to anterior teeth of 11-13 year old Thai children. Community Dent Health. 2006;23(4):222–7.
34. Naidoo S, Sheiham A, Tsakos G. Traumatic dental injuries of permanent incisors in 11- to 13-year-old South African schoolchildren. Dent Traumatol. 2009;25(2):224–8.

35. Nicolau B, Marcenes W, Sheiham A. The relationship between traumatic dental injuries and adolescents' development along the life course. Community Dent Oral Epidemiol. 2003;31(4):306–13.
36. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? Soc Sci Med. 1994;39(7):887–903.
37. Victora CG, Huttly SR, Fuchs SC, Olinto MTA. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int J Epidemiol. 1997;26(1):224–7.
38. Moysés ST, Camilotti AG, Vetorello M, Moysés SJ. Spatial analysis of dental trauma in 12-year-old schoolchildren in Curitiba, Brazil. Dent Traumatol. 2008;24(4):449–53.
39. Jorge KO, Moysés SJ, Ferreira E, Ramos-Jorge ML, PMP DAZ. Prevalence and factors associated to dental trauma in infants 1-3 years of age. Dent Traumatol. 2009;25(2):185–9.
40. Vettore MV, Efhima S, Machuca C, de Almeida Lamarca G. Income inequality and traumatic dental injuries in 12-year-old children: a multilevel analysis. Dent Traumatol. 2017;33(5):375–82.
41. Baghdady VS, Ghose LJ, Enke H. Traumatized anterior teeth in Iraqi and Sudanese children–a comparative study. J Dent Res. 1981;60(3):677–80.
42. Finney Lamb CE, Whelan AK, Michaels C. Refugees and oral health: lessons learned from stories of Hazara refugees. Aust Health Rev.
43. Marcenes W, Zabot N, Traebert J. Socio-economic correlates of traumatic injuries to the permanent incisors in schoolchildren aged 12 years in Blumenau, Brazil. Dent Traumatol. 2001; 17(5):222–6.
44. Perheentupa U, Laukkanen P, Veijola J, et al. Increased lifetime prevalence of dental trauma is associated with previous non-dental injuries, mental distress and high alcohol consumption. Dent Traumatol. 2001;17(1):10–6.
45. Soriano EP, Caldas AF, Angeiras Góes PS. Risk factors related to traumatic dental injuries in Brazilian schoolchildren. Dent Traumatol. 2004;20(5):246–50.
46. Kahabuka FK, Mugonzibwa EA. Risk factors for injuries to maxillary permanent incisors and upper lip among schoolchildren in Dar es Salaam, Tanzania. Int J Paediatr Dent. 2009;19(2):148–54.
47. David J, Åstrøm AN, Wang NJ. Factors associated with traumatic dental injuries among 12-year-old schoolchildren in South India. Dent Traumatol. 2009;25(5):500–5.
48. Navabazam A, Farahani SS. Prevalence of traumatic injuries to maxillary permanent teeth in 9- to 14-year-old school children in Yazd, Iran. Dent Traumatol. 2010;26(2):154–7.
49. Sgan-Cohen HD, Megnagi G, Jacobi Y. Dental trauma and its association with anatomic, behavioral, and social variables among fifth and sixth grade schoolchildren in Jerusalem. Community Dent Oral Epidemiol. 2005;33(3):174–80.
50. Livny A, Sgan-Cohen HD, Junadi S, Marcenes W. Traumatic dental injuries and related factors among sixth grade schoolchildren in four Palestinian towns. Dent Traumatol. 2010;26(5):330–4.
51. Oliveira LB, Marcenes W, Ardenghi TM, Sheiham A, Bönecker M. Traumatic dental injuries and associated factors among Brazilian preschool children. Dent Traumatol. 2007;23(2):76–81.
52. Granville-Garcia AF, De Menezes VA, De Lira PIC. Dental trauma and associated factors in Brazilian preschoolers. Dent Traumatol. 2006;22(6):318–22.
53. Stewart GB, Shields BJ, Fields S, Comstock RD, Smith GA. Consumer products and activities associated with dental injuries to children treated in United States emergency departments, 19902003. Dent Traumatol. 2009;25(4):399–405.
54. Hamilton FA, Hill FJ, Holloway PJ. An investigation of dento-alveolar trauma and its treatment in an adolescent population. Part 1 : the prevalence and incidence of injuries and the extent and adequacy of treatment received. Br Dent J. 1997;182(3): 91–5.
55. Marcenes W, Murray S. Changes in prevalence and treatment need for traumatic dental injuries among 14-year-old children in Newham, London: a deprived area. Community Dent Health. 2002;19(2):104–8.
56. Damé-Teixeira N, Alves LS, Susin C, Maltz M. Traumatic dental injury among 12-year-old South Brazilian schoolchildren: prevalence, severity, and risk indicators. Dent Traumatol. 2013;29(1):52–8.
57. Bendo CB, Paiva SM, Oliveira AC, et al. Prevalence and associated factors of traumatic dental injuries in Brazilian schoolchildren. J Public Health Dent. 2010;70(4):313–8.
58. Traebert J, Peres MA, Blank V, Da Silva BR, Pietruza JA. Prevalence of traumatic dental injury and associated factors among 12-year-old school children in Florianópolis, Brazil. Dent Traumatol. 2003;19(1):15–8.
59. Odoi R, Croucher R, Wong F, Marcenes W. The relationship between problem behaviour and traumatic dental injury amongst children aged 7-15 years old. Community Dent Oral Epidemiol. 2002;30(5):392–6.
60. Cortes MIS, Marcenes W, Sheiham A. Prevalence and correlates of traumatic injuries to the permanent teeth of schoolchildren aged 9-14 years in Belo Horizonte, Brazil. Dent Traumatol. 2001;17(1):22–6.
61. Feldens CA, Kramer PF, Feldens EG, Pacheco LM, Vítolo MR. Socioeconomic, behavioral, and anthropometric risk factors for traumatic dental injuries in childhood: a cohort study. Int J Paediatr Dent. 2014;24(3):234–43.
62. Moysés SJ, Moysés ST, McCarthy M, Sheiham A. Intra-urban differentials in child dental trauma in relation to healthy cities policies in Curitiba, Brazil. Health Place. 2006;12(1):48–64.
63. Pattussi MP, Hardy R, Sheiham A. Neighborhood social capital and dental injuries in Brazilian adolescents. Am J Public Health. 2006;96(8):1462–8.
64. Goettems ML, Brancher LC, da Costa CT, Bonow MLM, Romano AR. Does dental trauma in the primary dentition increases the likelihood of trauma in the permanent dentition? A longitudinal study. Clin Oral Investig. 2017;21(8):2415–20.
65. Federation Dentaire Internationale (FDI). Commission on dental products; 1990.
66. Ramchandani D, Marcenes W, Stansfeld SA, Bernabé E. Problem behaviour and traumatic dental injuries in adolescents. Dent Traumatol. 2016;32(1):65–70.
67. Lalloo R. Risk factors for major injuries to the face and teeth. Dent Traumatol. 2003;19(1):12–4.
68. Davidson LL, Taylor EA, Sandberg ST, Thorley G. Hyperactivity in school-age boys and subsequent risk of injury. Pediatrics. 1992;90(5):697–702.
69. Sabuncuoglu O. Traumatic dental injuries and attention-deficit/hyperactivity disorder: is there a link? Dent Traumatol. 2007;23(3):137–42.
70. Sabuncuoglu O, Taser H, Berkem M. Relationship between traumatic dental injuries and attention-deficit/ hyperactivity disorder in children and adolescents: proposal of an explanatory model. Dent Traumatol. 2005;21(5):249–53.
71. Basha S, Noor Mohammad R, Shivalinga SH. Incidence of dental trauma among obese adolescents – a 3-year-prospective study. Dent Traumatol. 2015;31(2):125–9.
72. Petti S, Tarsitani G. Traumatic injuries to anterior teeth in Italian schoolchildren: prevalence and risk factors. Endod Dent Traumatol. 1996;12(6):294–7.
73. Soriano EP, Caldas ADF, De Carvalho MVD, Amorim Filho HDA. Prevalence and risk factors related to traumatic dental injuries in Brazilian schoolchildren. Dent Traumatol. 2007;23(4):232–40.
74. Borges TS, Chaffee BW, Kramer PF, Feldens EG, Vítolo MRFC. Relationship between overweight/obesity in the first year

of age and traumatic dental injuries in early childhood: findings from a birth cohort study. Dent Traumatol. 2017;33(6):465–71.
75. Bessermann K. Frequency of maxillo-facial injuries in a hospital population of patients with epilepsy. Bull Nord Soc Dent Handicap. 1978;5:2–26.
76. Holan G, Peretz B, Efrat J, Shapira Y. Traumatic injuries to the teeth in young individuals with cerebral palsy. Dent Traumatol. 2005;21(2):65–9.
77. Miamoto CB, Ramos-Jorge ML, Ferreira MC, de Oliveira M, Vieira-Andrade RG, Marques LS. Dental trauma in individuals with severe cerebral palsy: prevalence and associated factors. Braz Oral Res. 2011;25(4):319–23.
78. Johnson JE. Causes of accidental injuries to the teeth and jaws. J Public Health Dent. 1975;35:123–31.
79. AlSarheed M, Bedi R, Hunt NP. Traumatised permanent teeth in 11-16-year-old Saudi Arabian children with a sensory impairment attending special schools. Dent Traumatol. 2003;19(3):123–5.
80. Paiva PCP, de Paiva HN, de Oliveira Filho PM, Côrtes MI de S. Prevalence and risk factors associated with traumatic dental injury among 12-year-old schoolchildren in Montes Claros, MG, Brazil. Cien Saude Colet. 2015;20(4):1225–33.
81. De Oliveira Filho PM, Jorge KO, Paiva PCP, Ferreira EF, Ramos-Jorge ML, Zarzar PM. The prevalence of dental trauma and its association with illicit drug use among adolescents. Dent Traumatol. 2014;30(2):122–7.
82. De Moor RJG, De Witte AMJC, De Bruyne MAA. Tongue piercing and associated oral and dental complications. Dent Traumatol. 2000;16(5):232–7.
83. Cox D, Vincent DG, McGwin G, MacLennan PA, Holmes JD, Rue LW. Effect of restraint systems on maxillofacial injury in frontal motor vehicle collisions. J Oral Maxillofac Surg. 2004;62(5):571–5.
84. Thompson DC, Rivara F, Thompson R. Helmets for preventing head and facial injuries in bicyclists. Cochrane Database Syst Rev. 1999;(2):CD001855.
85. Petti S. Over two hundred million injuries to anterior teeth attributable to large overjet: a meta-analysis. Dent Traumatol. 2015;31(1):1–8.
86. Elkarmi RF, Hamdan MA, Rajab LD, Abu-Ghazaleh SB, Sonbol HN. Prevalence of traumatic dental injuries and associated factors among preschool children in Amman, Jordan. Dent Traumatol. 2015;31(6):487–92.
87. Tello G, Bonini GC, Murakami C, Abanto J, Oliveira LB, Bönecker M. Trends in the prevalence of traumatic crown injuries and associated factors in Brazilian preschool children: 10-year observational data. Dent Traumatol. 2016;32(4):274–80.
88. Nguyen QV, Bezemer PD, Habets L, Prahl-Andersen B. A systematic review of the relationship between overjet size and traumatic dental injuries. Eur J Orthod. 1999;21(5):503–15.
89. Gupta S, Kumar-Jindal S, Bansal M, Singla A. Prevalence of traumatic dental injuries and role of incisal overjet and inadequate lip coverage as risk factors among 4-15 years old government school children in Baddi-Barotiwala area, Himachal Pradesh, India. Med Oral Patol Oral Cir Bucal.
90. Ain TS, Lingesha RT, Sultan S, et al. Prevalence of traumatic dental injuries to anterior teeth of 12-year-old school children in Kashmir, India. Arch Trauma Res. 2016;5(1):e24596.
91. Kramer PF, Pereira LM, Ilha MC, Borges TS, Freitas MPM, Feldens CA. Exploring the impact of malocclusion and dentofacial anomalies on the occurrence of traumatic dental injuries in adolescents. Angle Orthod. 2017;87(6):816–23.
92. Martins VM, Sousa RV, Rocha ES, Leite RB, Paiva SM, Granville-Garcia AF. Dental trauma among Brazilian schoolchildren: prevalence, treatment and associated factors. Eur Arch Paediatr Dent. 2012;13(5):232–7.
93. Patel M, Sujan S. The prevalence of traumatic dental injuries to permanent anterior teeth and its relation with predisposing risk factors among 8-13 years school children of Vadodara city: an epidemiological study. J Indian Soc Pedod Prev Dent. 2012;30(2):151.
94. Corrêa-Faria P, Paiva SM, Pordeus IA, Ramos-Jorge ML. Influence of clinical and socioeconomic indicators on dental trauma in preschool children. Braz Oral Res. 2015;29(1):1–7.
95. Agostini BA, Pinto LT, Koehler M, Emmanuelli B, Piovesan C, Ardenghi TM. Trend of traumatic crown injuries and associated factors in preschool children. Braz Oral Res. 2016;30(1):e112.
96. Hargreaves JA, Cleaton-Jones PE, Roberts GJ, Williams S, Matejka JM. Trauma to primary teeth of South African preschool children. Dent Traumatol. 1999;15(2):73–6.
97. Robson F, Ramos-Jorge ML, Bendo CB, Vale MP, Paiva SM, Pordeus IA. Prevalence and determining factors of traumatic injuries to primary teeth in preschool children. Dent Traumatol. 2009;25(1):118–22.
98. Dutra FT, Marinho AM, Godoi PFS, Borges CM, Ferreira EFE, Zarzar PM. Prevalence of dental trauma and associated factors among 1- to 4-year-old children. J Dent Child (Chic). 2010;77(3):146–51.
99. Viegas CM, Scarpelli AC, Carvalho AC, Ferreira FM, Pordeus IA, Paiva SM. Predisposing factors for traumatic dental injuries in Brazilian preschool children. Eur J Paediatr Dent. 2010;11(2):59–65.
100. Bonini GC, Bönecker M, Braga MM, Mendes FM. Combined effect of anterior malocclusion and inadequate lip coverage on dental trauma in primary teeth. Dent Traumatol. 2012;28(6):437–40.
101. Norton E, O'Connell AC. Traumatic dental injuries and their association with malocclusion in the primary dentition of Irish children. Dent Traumatol. 2012;28(1):81–6.
102. Siqueira MBLD, Gomes MC, Oliveira AC, Martins CC, Granville-Garcia AF, Paiva SM. Predisposing factors for traumatic dental injury in primary teeth and seeking of post-trauma care. Braz Dent J. 2013;24(6):647–54.
103. Antunes LA, Gomes I, Almeida M, Silva EB, Calasans-Maia JA, Antunes L. Increased overjet is a risk factor for dental trauma in preschool children. Indian J Dent Res. 2015;26(4):356.
104. Kramer PF, Feldens EG, Bruch CM, Ferreira SH, Feldens CA. Clarifying the effect of behavioral and clinical factors on traumatic dental injuries in childhood: a hierarchical approach. Dent Traumatol. 2015;31(3):177–83.
105. Marcenes W, Murray S. Social deprivation and traumatic dental injuries among 14-year-old schoolchildren in Newham, London. Dent Traumatol. 2001;17(1):17–21.
106. Traebert J, Almeida ICS, Garghetti C, et al. Prevalence, treatment needs, and predisposing factors for traumatic injuries to permanent dentition in 11-13-year-old schoolchildren. Cad Saude Publica. 2004;20(2):403–10.
107. Årtun J, Behbehani F, Al-Jame B, Kerosuo H. Incisor trauma in an adolescent Arab population: prevalence, severity, and occlusal risk factors. Am J Orthod Dentofac Orthop. 2005;128(3):347–52.
108. Carvalho ML, Moysés SJ, Bueno RE, Shimakura S, Moysés ST. A geographical population analysis of dental trauma in school-children aged 12 and 15 in the city of Curitiba-Brazil. BMC Health Serv Res. 2010;10:203.
109. Taiwo OO, Jalo HP. Dental injuries in 12-year old Nigerian students. Dent Traumatol. 2011;27(3):230–4.
110. Bendo CB, Vale MP, Figueiredo LD, Pordeus IA, Paiva SM. Social vulnerability and traumatic dental injury among Brazilian schoolchildren: a population-based study. Int J Environ Res Public Health. 2012;9(12):4278–91.

111. Jorge KO, Oliveira Filho PM, Ferreira EF, Oliveira AC, Vale MP, Zarzar PM. Prevalence and association of dental injuries with socioeconomic conditions and alcohol/drug use in adolescents between 15 and 19years of age. Dent Traumatol. 2012;28(2):136–41.
112. Schatz JP, Hakeberg M, Ostini E, Kiliaridis S. Prevalence of traumatic injuries to permanent dentition and its association with overjet in a Swiss child population. Dent Traumatol. 2013;29(2):110–4.
113. Al-Bajjali TT, Rajab LD. Traumatic dental injuries among 12-year-old Jordanian schoolchildren: an investigation on obesity and other risk factors. BMC Oral Health. 2014;14(1):101.
114. Chopra A, Lakhanpal M, Rao N, Gupta N, Vashisth S. Traumatic dental injuries among 12-15-year-old-school children in Panchkula. Arch Trauma Res. 2014;3(1):e18127.
115. de Lourdes Vieira Frujeri M, JAJ F, ACB B, de Souza Gruppioni Cortes MI, Dias Costa E. Socio-economic indicators and predisposing factors associated with traumatic dental injuries in schoolchildren at Brasília, Brazil: a cross-sectional, population-based study. BMC Oral Health. 2014;14(1):91.
116. do Carmo Matias Freire M, Vasconcelos DN, dos Santos Vieira A, Araújo JA, da Silveira Moreira R, de Fátima Nunes M. Association of traumatic dental injuries with individual-, sociodemographic- and school-related factors among schoolchildren in Midwest Brazil. Int J Environ Res Public Health. 2014;11(9):9885–96.
117. Bilder L, Margvelashvili V, Sgan-Cohen H, et al. Traumatic dental injuries among 12- and 15-year-old adolescents in Georgia: results of the pathfinder study. Dent Traumatol. 2016;32(3):169–73.
118. Mathur MR, Watt RG, Millett CJ, Parmar P, Tsakos G. Determinants of socioeconomic inequalities in traumatic dental injuries among urban Indian adolescents. PLoS One. 2015;10(10):e0140860.
119. Garg K, Kalra N, Tyagi R, Khatri A, Panwar G. An appraisal of the prevalence and attributes of traumatic dental injuries in the permanent anterior teeth among 7–14-year-old school children of north East Delhi. Contemp Clin Dent. 2017;8(2):218.
120. Silva-Oliveira F, Goursand D, Ferreira RC, et al. Traumatic dental injuries in Brazilian children and oral health-related quality of life. Dent Traumatol. 2018;34(1):28–35.
121. Sischo L, Broder HL. Oral health-related quality of life: what, why, how, and future implications. J Dent Res. 2011;90(11):1264–70.
122. Zaror C, Martínez-Zapata MJ, Abarca J, et al. Impact of traumatic dental injuries on quality of life in preschoolers and schoolchildren: a systematic review and meta-analysis. Community Dent Oral Epidemiol. 2018;46(1):88–101.
123. Ramos-Jorge J, Sá-Pinto AC, Almeida Pordeus I, Martins Paiva S, Castro Martins C, Ramos-Jorge ML. Effect of dark discolouration and enamel/dentine fracture on the oral health-related quality of life of pre-schoolers. Eur Arch Paediatr Dent. 2017;18(2):83–9.
124. Aldrigui JM, Abanto J, Carvalho TS, et al. Impact of traumatic dental injuries and malocclusions on quality of life of young children. Health Qual Life Outcomes. 2011;9:78.
125. Viegas CM, Scarpelii AC, Carvalho AC, de Morais Ferreira F, Pordeus IA, Paiva SM. Impact of traumatic dental injury on quality of life among Brazilian preschool children and their families. Pediatr Dent. 2012;34(4):300–6.
126. Kramer PF, Feldens CA, Helena Ferreira S, Bervian J, Rodrigues PH, Peres MA. Exploring the impact of oral diseases and disorders on quality of life of preschool children. Community Dent Oral Epidemiol. 2013;41(4):327–35.
127. Gomes MC, Pinto-Sarmento TCDA, EMMDB C, Martins CC, Granville-Garcia AF, Paiva SM. Impact of oral health conditions on the quality of life of preschool children and their families: a cross-sectional study. Health Qual Life Outcomes. 2014;12:55.
128. Guedes RS, Piovesan C, Antunes JLF, Mendes FM, Ardenghi TM. Assessing individual and neighborhood social factors in child oral health-related quality of life: a multilevel analysis. Qual Life Res. 2014;23(9):2521–30.
129. Viegas CM, Paiva SM, Carvalho AC, Scarpelli AC, Ferreira FM, Pordeus IA. Influence of traumatic dental injury on quality of life of Brazilian preschool children and their families. Dent Traumatol. 2014;30(5):338–47.
130. Abanto J, Tello G, Bonini GC, Oliveira LB, Murakami C, Bönecker M. Impact of traumatic dental injuries and malocclusions on quality of life of preschool children: a population-based study. Int J Paediatr Dent. 2015;25(1):18–28.
131. Firmino RT, Gomes MC, Clementino MA, Martins CC, Paiva SM, Granville-Garcia AF. Impact of oral health problems on the quality of life of preschool children: a case–control study. Int J Paediatr Dent. 2016;26(4):242–9.
132. Vieira-Andrade RG, Siqueira MBL, Gomes GB, et al. Impact of traumatic dental injury on the quality of life of young children: a case-control study. Int Dent J. 2015;65(5):261–8.
133. Gomes MC, Neves ÉTB, Perazzo MF, Paiva SM, Ferreira FM, Granville-Garcia AF. Contextual and individual determinants of oral health-related quality of life among five-year-old children: a multilevel analysis. PeerJ. 2018;6:e5451.
134. Ramos-Jorge J, Paiva SM, Tataounoff J, Pordeus IA, Marques LS, Ramos-Jorge ML. Impact of treated/untreated traumatic dental injuries on quality of life among Brazilian schoolchildren. Dent Traumatol. 2014;30(1):27–31.
135. Antunes LAA, Antunes LDS, Luiz RR, Leão ATT, Maia LC. Assessing the responsiveness of the Brazilian FIS to treatment for traumatic dental injury. Community Dent Oral Epidemiol. 2013;41(6):551–7.
136. Locker D. Disparities in oral health-related quality of life in a population of Canadian children. Community Dent Oral Epidemiol. 2007;35(5):348–56.
137. Bendo CB, Paiva SM, Torres CS, et al. Association between treated/untreated traumatic dental injuries and impact on quality of life of Brazilian schoolchildren. Health Qual Life Outcomes. 2010;8:114.
138. Piovesan C, Abella C, Ardenghi TM. Child oral health-related quality of life and socioeconomic factors associated with traumatic dental injuries in schoolchildren. Oral Health Prev Dent. 2011;9(4):405–11.
139. Paula JS, Leite ICG, Almeida AB, Ambrosano GMB, Pereira AC, Mialhe FL. The influence of oral health conditions, socioeconomic status and home environment factors on schoolchildren's self-perception of quality of life. Health Qual Life Outcomes. 2012;10:6.
140. Traebert J, de Lacerda JT, Foster Page LA, Thomson WM, Bortoluzzi MC. Impact of traumatic dental injuries on the quality of life of schoolchildren. Dent Traumatol. 2012;28(6):423–8.
141. Damé-Teixeira N, Alves LS, Ardenghi TM, Susin C, Maltz M. Traumatic dental injury with treatment needs negatively affects the quality of life of Brazilian schoolchildren. Int J Paediatr Dent. 2013;23(4):266–73.
142. Bendo CB, Paiva SM, Abreu MH, Figueiredo LD, Vale MP. Impact of traumatic dental injuries among adolescents on family's quality of life: a population-based study. Int J Paediatr Dent. 2014;24(5):387–96.
143. Pulache J, Abanto J, Oliveira LB, Bönecker M, Porras JC. Exploring the association between oral health problems and oral health-related quality of life in Peruvian 11- to 14-year-old children. Int J Paediatr Dent. 2016;26(2):81–90.
144. Bomfim RA, Herrera DR, De-Carli AD. Oral health-related quality of life and risk factors associated with traumatic dental

injuries in Brazilian children: a multilevel approach. Dent Traumatol. 2017;33(5):358–68.
145. El-Kalla I, Shalan H, Bakr R. Impact of dental trauma on quality of life among 11–14 years schoolchildren. Contemp Clin Dent. 2017;8(4):538.
146. Martins MT, Sardenberg F, Bendo CB, et al. Dental caries remains as the main oral condition with the greatest impact on children's quality of life. PLoS One. 2017;12(10):e0185365.
147. Martins MT, Sardenberg F, Bendo CB, Vale MP, Paiva SM, Pordeus IA. Dental caries are more likely to impact on children's quality of life than malocclusion or traumatic dental injuries. Eur J Paediatr Dent. 2018;19(3):194–8.
148. Keles S, Abacigil F, Adana F. Oral health status and oral health related quality of life among adolescent workers. Clujul Med. 2018;91(4):462–8.
149. Soares JP, Barasuol JC, Torres FM, et al. The impact of crown fracture in the permanent dentition on children's quality of life. Dent Traumatol. 2018;34(3):158–63.
150. World Health Organization. The world health report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization; 2002.
151. Feldens EG, Feldens CA, Kramer PF, da Silva KG, Munari CC, Brei VA. Understanding school teacher's knowledge regarding dental trauma: a basis for future interventions. Dent Traumatol. 2010;26(2):158–63.
152. Al-Musawi A, Al-Sane M, Andersson L. Smartphone App as an aid in the emergency management of avulsed teeth. Dent Traumatol. 2017;33(1):13–8.
153. de Almeida GR, de Lucas Rezende LVM, da- Silva CQ, JCF A. Remote diagnosis of traumatic dental injuries using digital photographs captured via a mobile phone. Dent Traumatol. 2017;33(5):350–7.
154. Mohan A, Agarwal T, Cherian TS, et al. Diagnostic ability of a smart phone app (injured tooth) in diagnosing traumatic injuries to the teeth – a multicentre analysis. Int J Paediatr Dent. 2018;28(6):561–9.
155. Djemal S, Singh P. Smartphones and dental trauma: the current availability of apps for managing traumatic dental injuries. Dent Traumatol. 2016;32(1):52–7.
156. Bücher K, Neumann C, Thiering E, Hickel R, Kühnisch J. Complications and survival rates of teeth after dental trauma over a 5-year period. Clin Oral Investig. 2013;17(5):1311–8.
157. Day, P, Flores, MT, O'Connell, A, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 3. Injuries in the primary dentition. Dent Traumatol. 2020; 36: 343–59.
158. Wang G, Wang C, Qin M. Pulp prognosis following conservative pulp treatment in teeth with complicated crown fractures—a retrospective study. Dent Traumatol. 2017;33(4):255–60.
159. Lauridsen E, Blanche P, Amaloo C, Andreasen JO. The risk of healing complications in primary teeth with concussion or subluxation injury—a retrospective cohort study. Dent Traumatol. 2017;33(5):337–44.
160. Fried I, Erickson DDSP, Schwartz S, Keenan MK. Subluxation injuries of maxillary primary anterior teeth: epidemiology and prognosis of 207 traumatized teeth. Pediatr Denst. 1996;18(2):145–51.
161. Cunha RF, Pugliesi DMC, Percinoto C. Treatment of traumatized primary teeth: a conservative approach. Dent Traumatol. 2007;23(6):360–3.
162. Cho WC, Nam OH, Kim MS, Lee HS, Choi SC. A retrospective study of traumatic dental injuries in primary dentition: treatment outcomes of splinting. Acta Odontol Scand. 2018;76(4):253–6.
163. Lauridsen E, Blanche P, Yousaf N, Andreasen JO. The risk of healing complications in primary teeth with extrusive or lateral luxation—a retrospective cohort study. Dent Traumatol. 2017;33(4):307–16.
164. Spinas E, Melis A, Savasta A. Therapeutic approach to intrusive luxation injuries in primary dentition. A clinical follow-up study. Eur J Paediatr Dent. 2006;7(4):179–86.
165. Colak I, Markovic D, Petrovic B, Peric T, Milenkovic A. A retrospective study of intrusive injuries in primary dentition. Dent Traumatol. 2009;25(6):605–10.
166. Lauridsen E, Blanche P, Yousaf N, Andreasen JO. The risk of healing complications in primary teeth with intrusive luxation: a retrospective cohort study. Dent Traumatol. 2017;33(5):329–36.
167. Hinckfuss SE, Messer LB. An evidence-based assessment of the clinical guidelines for repanted avulsed teeth. Part I: timing of pulp extirpation. Dent Traumatol. 2009a;25(1):32–42.
168. Hinckfuss SE, Messer LB. An evidence-based assessment of the clinical guidelines for replanted avulsed teeth. Part II: prescription of systemic antibiotics. Dent Traumatol.
169. Hinckfuss SE, Messer LB. Splintig duration and periodontal outcomes for replanted avulsed teeth: a systematic review. Dent Traumatol. 2009c;25(2):150–7.
170. Petrovic B, Marković D, Peric T, Blagojevic D. Factors related to treatment and outcomes of avulsed teeth. Dent Traumatol. 2010;26(1):52–9.
171. Fouad, AF, Abbott, PV, Tsilingaridis, G, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 2. Avulsion of permanent teeth. Dent Traumatol. 2020; 36: 331–42.
172. Hobdell M, Petersen PE, Clarkson J, Johnson N. Global goals for oral health 2020. Int Dent J. 2003;53(5):285–8.
173. Watt RG. Strategies and approaches in oral disease prevention and health promotion. Bull World Health Organ. 2005;83(9):711–8.

Further Reading

Andreasen JO, Lauridsen E, Andreasen FM. Contradictions in the treatment of traumatic dental injuries and ways to proceed in dental trauma research. Dent Traumatol. 2010;26(1):16–22.
Andreasen JO, Lauridsen E, Gerds TA, Ahrensburg SS. Dental trauma guide: a source of evidence-based treatment guidelines for dental trauma. Dent Traumatol. 2012;28(5):345–50.
Feldens CA, Kramer PF, Feldens EG. Exploring the profile of articles on traumatic dental injuries in pediatric dental journals. Dent Traumatol. 2013;29(3):172–7.
Glendor U. Epidemiology of traumatic dental injuries--a 12 year review of the literature. Dent Traumatol. 2008;24(6):603–11.
International Association of Dental Traumatology. Dental trauma guide. Available at https://dentaltraumaguide.org/
Kenny KP, Day PF, Sharif MO, et al. What are the important outcomes in traumatic dental injuries? An international approach to the development of a core outcome set. Dent Traumatol. 2018;34(1):4–11.
Petti S, Glendor U, Andersson L. World traumatic dental injury prevalence and incidence, a meta-analysis-One billion living people have had traumatic dental injuries. Dent Traumatol. 2018;34(2):71–86.

Epidemiology of Cleft Lip and Palate

Kaye Roberts-Thomson

Contents

9.1 Introduction – 160

9.2 Embryology – 160

9.3 Considerations – 160

9.4 International Birth Incidence/Prevalence – 160
9.4.1 Ethnicity – 161
9.4.2 Sex – 161

9.5 Environmental Risk Factors – 161
9.5.1 Smoking – 161
9.5.2 Alcohol – 162
9.5.3 Folic Acid Intake – 162
9.5.4 Maternal Obesity – 162
9.5.5 Maternal Stress – 163
9.5.6 Maternal Health – 163
9.5.7 Socio-economic Status – 163
9.5.8 Population Attributable Risk – 163

9.6 Genetics – 164
9.6.1 Genetic-Environmental Interactions – 164

9.7 Quality of Life – 164
9.7.1 Health Outcomes – 165

9.8 Conclusion – 165

References – 165

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_9

Key Points

- Cleft lip +/– cleft palate is a common birth defect.
- Frequency varies with ethnicity and social circumstances.
- There is mixed evidence in relation to aetiology, maternal smoking being the only consistent finding.
- Some associations are found among genes, genetic-environmental and gene-gene interactions.
- Untreated clefts result in high levels of disadvantage.
- Additional research is needed for effective preventive advice.
- Urgent need for equitable access to appropriate treatment.

Learning Objectives

- To understand the complexity of examining the aetiology of oral facial clefts
- To discuss the international prevalence of orofacial cleft and the difficulties with the data
- To identify the main environmental factors associated with orofacial clefts
- To explain the role of genes in the aetiology of orofacial clefts

9.1 Introduction

Orofacial clefts are some of the most common birth defects, and their prevalence has been documented among many populations. They have multiple risk factors and are polygenic in aetiology.

There is now an international register, the International Perinatal Database of Typical Orofacial Clefts (IPDTOC) which enables comparison of prevalence rates between different countries. However, one must be cautious about comparisons because of a lack of standardisation for inclusion and exclusion criteria. In addition many countries do not have national registers for birth defects and thus are not included in the database. Orofacial clefts may occur as cleft lip with or without a cleft palate (CLP) or as cleft palate alone (CPO). In addition cleft lip may occur unilaterally or bilaterally.

These orofacial clefts may be isolated defects and part of multiple congenital conditions (MCC) or arise in association with a syndrome. CPO seems to occur more frequently with MCC, and over 200 syndromes have been recognised which include orofacial clefts [1]. Orofacial clefts carry with them significant morbidity often associated with difficulty in speech and hearing, with an increased morbidity and mortality throughout life [1].

9.2 Embryology

The embryological development of the upper lip and primary and secondary palate occurs from the 5th to 9th weeks of gestation, and the mother may not know she is pregnant by time of fusion of processes. In the 5th week, the right and left maxillary processes grow medially towards each other, and, at the same time, the frontonasal process descends to meet them. Together they form the upper lip, philtrum, the incisor alveolus and the triangular primary palate, and any failure of fusion can result in unilateral or bilateral cleft lip and/or alveolar and palatal cleft. Shortly after, during weeks 6 and 7, the right and left palatal protuberances stop descending and turn to grow horizontally towards each other, meeting at the midline from anterior to posterior, thus forming the secondary palate which fuses with the primary palate. At the same time, the developing tongue needs to move forward and downward to permit the palatal shelves to meet each other. Interruptions to the fusion process or delay in tongue descent will lead to cleft formation. From the timing of these developments, it can be seen that by the time of pregnancy confirmation, it is too late to institute preventive measures such as folate supplements.

9.3 Considerations

Apparent differences in rates and in estimation of risk factors are complicated by differing criteria such as inclusion or non-inclusion of syndromic and/or MMC data with isolated clefts and whether isolated clefts include cleft lip with or without cleft palate and cleft palate alone. The source of the population under discussion may vary, between hospital birth or ultrasound data and population data banks. Here again data may or may not include termination of pregnancy data. Timing of the assessment and the completeness of the data are also potential issues. Differing measurements of exposures are also evident particularly in smoking and alcohol use.

In addition both cohort and case control studies exist in the literature with the majority being case control studies which have the attendant risk of recall bias. Unless otherwise indicated the following refers to isolated or non-syndromic cases.

9.4 International Birth Incidence/ Prevalence

There is a variety of epidemiological terminologies in the literature. As it is impossible to ascertain the numbers of orofacial defects where the pregnancy is spontaneously aborted, true incidence cannot be measured. In

many countries termination of pregnancy is not permitted or not reported, or the reasons for termination are not collected; in those situations data on the occurrence of orofacial clefts is not available. Hence the terms most commonly in use are birth prevalence or birth incidence, indicating the recognition of the defect at birth.

The IPDTOC report on the prevalence at birth of cleft lip with or without cleft palate [2] which reported data from 54 registries in 30 countries found the overall prevalence at 9.92 per 10,000 (varying from 5.02 to 23.85 per 10,000 live births). The data included live-births, still births and terminations where available. Cleft lip accounted for 3.32 per 10,000 and cleft lip and palate for 6.64 per 10,000. Over three quarters were isolated cases (76.8%), 15.9% had MMC, and 7.3% were syndromic.

This same article reported higher birth prevalence of total orofacial clefts in Japan, Mexico, South America, Western Europe and Canada and lower prevalence in Eastern Europe, South-Mediterranean Europe and South Africa. Isolated cases were more prevalent in Eastern Europe. Isolated cases were associated with increasing latitude in Europe and with longitude increasing towards the west in North America. However, comparing prevalence across different countries is not straightforward due to a lack of standardisation in inclusion and exclusion criteria.

Chinese and Indian data were not available to the IPDTOC study and are presented here. A meta-analysis of Chinese data [3] found a prevalence of 1.67 per thousand for non-syndromic orofacial clefts with a wide variation between provinces from 4.7 per 1000 in Hainan to 0.9 per 1000 in Shandong. Wang et al. (2017) [4] in a review of 41 studies from 1986 to 2015 reported a prevalence of 1.4 per thousand births. The authors suggest that the differences may be related to differences in environmental pollution, economic status, health service status and diagnostic level. Balaji (2018) [5] reported a prevalence of 3.3 per 1000 for non-syndromic clefts in India.

9.4.1 Ethnicity

Within country differences have also been found between American Indian/Alaskan Natives and non-Hispanic whites [6] with a 70% higher rate among American Indians/Alaskan Natives. Ethnic differences have also been noted in New Zealand. Thompson et al. (2016) [7] reported an overall birth prevalence of 1.77 per thousand, with rates for European and Pacific populations of 1.64 and 1.66 per 1000 live births, respectively, compared to 2.37 per 1000 live births for Māori. The Māori high rate is related to the elevated prevalence of CPO in this population of 1.54 per 1000 compared to 0.73 per thousand in the European population.

9.4.2 Sex

Almost all studies report a higher prevalence of CPO in females and for CLP in males, although the sex ratio varies with severity of the cleft, presence of additional malformations with clefts in boys being more frequent when associated with other abnormalities, the number of affected siblings in a family and ethnic origin [8].

9.5 Environmental Risk Factors

About 20% of OFC cases have a family history [9], and over 200 syndromes include OFC as one of the clinical features [1]. Nevertheless, the majority of cases are isolated or non-syndromic cases, suggesting an important role for environmental exposures in the aetiology. Most studies of orofacial anomalies have taken place in Western countries, with easier access to modern health information systems [2]. As highlighted by IPDTOC, very little information exists from developing countries.

9.5.1 Smoking

Maternal smoking has been consistently recognised as a risk factor for non-syndromic orofacial clefts [10–14]. Raut et al. (2018) [15] reported that maternal smoking during the month prior to pregnancy or the first month of pregnancy was the risk factor with the highest average-adjusted attributable risk for orofacial clefts (4.0% for CLP and 3.4% for CPO).

Passive smoking has also been implicated as a risk factor in a study [12] which examined the effect of passive smoking among non-smoking mothers (OR = 1.14, 95% CI: 1.02,1.27) and among smoking mothers exposed to environmental smoke which further increased the risk of orofacial clefts (OR = 1.51, 95% CI: 1.35, 1.70). A systematic review and meta-analysis by Sabbagh et al. (2015) [16] on maternal passive smoking and the risk of non-syndromic orofacial clefts found increased odds of orofacial clefts with passive smoking (OR 1.5) that were similar to those found for smoking.

A recent study by Wehby et al. (2017) [14] reported a negative interaction between body mass index (BMI) and maternal smoking with the largest risk associated with smoking for underweight mothers.

9.5.2 Alcohol

While there is agreement that alcohol may be teratogenic, findings on the relationship with orofacial clefts have been inconsistent.

DeRoo et al. (2016) [17] found mothers who drank an average of five plus drinks/sitting were more likely to deliver an infant with cleft lip only (pooled OR 1.48; 95% confidence intervals 1.01, 2.18) than mothers who did not drink alcohol. In a meta-analysis of five studies, Molina-Solana et al. (2013) [18] found significantly higher odds of 1.28 for the association between alcohol use and CLP. Other studies have also found a positive association [19].

However Bell et al. (2014) [20] in a meta-analysis of 18,349 participants in 13 studies of prenatal and pregnancy use of alcohol found no association between alcohol consumption during pregnancy and OFCs in infants. Romitti et al. (2007) [21] also found no association for alcohol generally but differences with type of alcohol with higher odds for the consumption of spirits. There was an interaction with folic acid intake.

Variation in relation to alcohol exposure measurements and inclusion of other risk factors in the analyses as well as data sources may account for some of the variation in results.

9.5.3 Folic Acid Intake

Low levels of folate in early pregnancy and pre-pregnancy have been recognised as an important risk factor for birth defects particularly neural tube defects. Hence folic acid supplementation pre-pregnancy and during the first trimester is a recommended practice in many countries. There has been interest in folate levels and orofacial clefts. However, the results have been mixed. In a recent study, Bezerra et al. [22] (2015) have shown that folate concentrations were lower in both children with a cleft ($p = 0.0001$) and mothers $p = 0.003$ than in controls. However, Ito (2018) [23] was unable to demonstrate a relationship between maternal folate levels and birth defects using serum folate levels at 18 weeks of pregnancy.

A number of studies have found supplementation with folic acid to be beneficial in preventing orofacial clefts. Folic acid was suggested as beneficial by Van Rooij et al. [24] in a study in the Netherlands (2004); folic acid supplementation taken 4 weeks prior to pregnancy until the 8th week of pregnancy was protective for orofacial clefts (OR 0.58; 95% CI 0.37–0.89). Wilcox et al. (2007) [25] conducted a Norwegian case control study in which they found evidence that a daily folic acid supplement of 400 mg or more per day was protective for CLP (OR 0.83; 95% CI 0.64–1.07).

Other studies found a difference in the effect of supplementation on the type of cleft. Butali et al. [26] and Millacura et al. (2017) [27] found a significant preventive effect with folic acid supplementation only for non-syndromic CLP. However, a meta-analysis [19] (6 cohort and 31 case control studies) determined that maternal folate supplementation was associated with a modest but statically significant decreased risk of all cleft subtypes (OR = 0.69, 95% CI: 0.60, 0.78). Folic acid intake alone was inversely associated with CL/P (OR = 0.73, 95% CI: 0.62–0.85) but to a lesser extent than CPO (OR = 0.75, 95% CI = 053–1.04).

In contrast, a Cochrane review [28] of folate supplementation found no statistically significant evidence of a preventive effect on cleft palate or cleft lip; however, only three studies met inclusion criteria for the analyses.

Johnson et al. (2008) [29] suggest that a distinction needs to be made between use of multivitamins and folate supplementation alone. Butali [26] examined multivitamin use and found a statistically significant reduction in risk of CLP with use of supplements containing folic acid ($p = 0.028$; OR = 0.80, 95% CI:0.66–0.98). Likewise, multivitamin intake had a significant protective effect for CLP (OR = 0.65 95% CI = 0.55–0.80) as well as CPO (OR = 0.69, 95% CI = 0.53–0.90) in a recent meta-analysis by Xu et al. [19].

The variation in results may be related to differing concentrations of folate either in the serum or the supplement. Alternatively it may be explained by differing genes present in the mother which interact with the folic acid.

9.5.4 Maternal Obesity

Maternal obesity is a risk factor in pregnancy for gestational diabetes and hypertension. There has also been concern about negative effects on the infant.

A number of studies have found an association between maternal weight and CLP and CPO. Stothard et al. [30] (2009) reported a small increased risk of both CLP and CPO for children of obese mothers as well as other congenital abnormalities. While a meta-analysis by Molina-Solana et al. [18] (2013) found obesity increased the risk for CLP by 26%, Block et al. [31] (2013) have found a dose-response effect with increasing BMI among obese women leading to increased risk of child orofacial defects.

Underweight has also been found to be a risk factor for orofacial clefts. While Kutbi et al. [32] (2017) found that both CP + CL and CPO were associated with a body mass index of greater than 35 compared with normal weight. The authors also found maternal underweight was marginally associated with cleft palate with or without cleft lip but that cleft lip alone was not asso-

ciated with BMI. As mentioned above Wehby and colleagues [14] found an interaction between smoking and maternal weight with smoking having a greater impact on the risk of CLP in underweight women. This indicates the importance of careful consideration of many factors together in understanding environmental risks.

9.5.5 Maternal Stress

High levels of maternal stress can affect maternal well-being and pregnancy outcomes either directly or through the effect of coping mechanisms used by the pregnant woman such as increased smoking or alcohol use. Carmichael et al. [33] (2007) reported a study of periconceptional stressful events and CLP and CPO. Stress was assessed using an 18 item questionnaire. The odds for orofacial clefts increased with increasing numbers of stressful events. A meta-analysis [18] also found that stressful events were associated with CLP (OR 1.41).

A retrospective study of the effects of Hurricane Katrina in New Orleans [34] found that the rate of orofacial clefts increased post the event relative to the earlier period. The effect was greater among Blacks than among non-Hispanic whites. Stress and possible teratogenic factors may account for this according to the authors.

9.5.6 Maternal Health

Health of the mother and medications taken during pregnancy have each been associated with orofacial clefts.

Waller et al. [35] 2017 found an increased risk of CLP of 1.23 (95%CI 1.05–1.45) among children from mothers who had experienced a cold or flu with a fever compared to those with no fever. This confirmed work by Dreier et al. [36] (2014) and Molina-Solana et al. [18] (2013) with increased risk from fever in first trimester for orofacial clefts in meta-analyses. Howley et al. [37] (2018) examined the relationship between self-reported genito-urinary tract infections and risk of birth defects in the month before conception and the first 3 months of pregnancy. Any genito-urinary infection either sexually transmitted or urinary tract infection was associated with cleft lip only.

Anti-epileptic drugs have been implicated in risk for orofacial clefts. Holmes et al. [38] (2012) suggested an increased risk of CLP among infants who were exposed to topiramate, an anticonvulsant drug. Likewise, Krapels et al. [39] (2006) found that maternal medication in the period around conception was related to CLP risk in the infant, although specific drugs responsible could not be identified.

9.5.7 Socio-economic Status

Research findings on the relationship between orofacial clefts and socio-economic status have been inconsistent both with individual and with neighbourhood measures.

Individual and neighbourhood measures of low socio-economic status were not associated with risk of orofacial clefts in a study by Carmichael et al. [40] (2003). However, Clark et al. [41] (2003) found a strong positive relationship between the prevalence of orofacial clefts at birth and increasing deprivation in Scotland. This trend was statistically significant for CLP but not CPO. Similarly, Durning et al. [42] (2007) reported a statistically significant risk for orofacial clefts between most and least deprived septiles of deprivation in Wales. Lupo et al. [43] (2015) also found that in Texas, mothers with children with orofacial clefts were more likely to live in deprived neighbourhoods than mothers with unaffected offspring. This association was strongest among Hispanic mothers.

Pawluk et al. [44] (2018) reported that low individual socio-economic status (SES) slightly increased the risk for CLP, but not a deprived neighbourhood. There was no interaction between individual SES and deprived neighbourhood. Similarly, Figueiredo et al. [45](2015) in an examination of individual risk factors for CLP and CPO in a multinational population from the developing world found that low maternal education and low paternal education were positively associated relative to higher levels of education.

9.5.8 Population Attributable Risk

Raut et al. [15] (2018) assessed the proportion of orofacial clefts attributable to modifiable risk factors. Using population attributable risk modelling, they found that non-modifiable risk factors contributed most to the model. Male sex contributed 26.53% and maternal non-Hispanic ethnicity 7.32% to the model for CLP; and female sex contributed 16.43% and maternal non-Hispanic ethnicity 13.49% to the model for CPO. However the modifiable risks each contributed less than 3% for both conditions with maternal smoking and lack of folic acid supplementation and maternal education less than high school contributing most.

For CLP the total contribution of the environmental factors was 50.40% and for CPO 42.97%. This indicates that either genetic factors, other unrecognised risk factors or genetic environment interactions make a substantial contribution to the aetiology of orofacial clefts. This study also indicates that programmes targeting maternal smoking are likely to have the most preventive impact on the prevalence of orofacial clefts.

9.6 Genetics

The genetic influence on the occurrence of isolated CLP and CPO was initially suggested by the increased risk of recurrence in first-degree relatives. For example, occurrence is more common in monozygotic twins (concordance 40–60%) than in dizygotic pairs (concordance 3–5%) [46]. Recurrence of clefts in siblings and offspring of affected individuals is about 4% which is higher than in the non-affected populations [47]. However, genetic studies have found many genes linked to CLP and CPO and have suggested that factors other than genotypes are required.

With recent advance in genetic technology including the mapping of the human genome, researchers have been able to investigate the association of individual gene variation with clefts as well as the interaction between genetic and environmental factors.

Although few genes have been shown consistently to be associated with orofacial clefts, there has been variation in consistent identification of some with the technical approach used and the population examined. Examining candidate genes and undertaking genome-wide investigations are two of the approaches used by geneticists to examine the associations.

A summary of the genetic influences on CLP derived from reviews by Dixon et al. [48] (2011), Rahimov et al. [46] (2012) and Leslie et al. [49] (2013) is outlined in Table 9.1. The influence of MAFB and ABCA4 has been found to be stronger in Asian populations and 8q24 in Caucasian populations [49].

As is true for many complex traits, substantial progress in gene-identification has occurred in the OFC field in the recent years. Technological advances and collaborative efforts have led to major advances in gene mapping for OFC, with the first wave of genome-wide association studies identifying several key candidate genes and loci [46, 48, 49]. By contrast, it is still unclear how genetic and environmental risk factors interact to elevate the risk of orofacial clefts, with only a few genetic-environmental (GxE) interactions having been uncovered [50]. The other area of future interest is gene x gene interactions [51].

9.6.1 Genetic-Environmental Interactions

Feldkamp et al. [52] (2015) suggested that there may be a difference between true teratogens and environmental factors which increase the predisposition towards having a child with a birth defect. Such distinctions have yet to be identified. Large numbers of subjects from a variety of populations will be needed in such genomic and environmental studies.

Table 9.1 Genes identified as associated with isolated orofacial clefts

Gene and genetic pathways and locations	Review
IRF6[a]	Dixon, Rahimov, Leslie
FOXE1[b]	Dixon, Rahimov
8q24 location	Dixon, Leslie
MAFB[c]	Dixon, Leslie
ABCA4[d] (location)	Dixon, Leslie
VAX1[e] (10q25 location)	Dixon, Leslie
MSX1[f]	Rahimov, Leslie
BMP[g] pathway	Rahimov, Leslie
FGF[h] pathway	Dixon, Rahimov

[a]Interferon regulatory factor 6
[b]Forkhead box 1
[c]V-maf musculoaponeurotic fibrosarcoma oncogene homologue B
[d]ATP-binding cassette, subfamily A 1
[e]Ventral anterior homeobox 1
[f]Msh homeobox 1
[g]Bone morphogenetic protein
[h]Fibroblast growth factor

Smoking, alcohol and folic acid may each interact with particular genes associated with orofacial clefts, but definitive associations require more investigation.

9.7 Quality of Life

Having a CLP or CPO affects the quality of life of affected individuals. Initially, infant feeding may be difficult and, in environments without early surgical interventions, may lead to malnourishment and possibly death. Balaji [5] (2018) cites an article [53] reporting that 18.76% of Indian children with orofacial clefts are left untreated.

Speech development may also be affected requiring speech therapy. Many children require specialised dental treatment as well. Surgical treatments, which may be multiple, dental and speech therapy, mean that the economic costs of repair and treatments can be substantial.

A systematic review and meta-analysis by Corrêa de Queiroz Herkrath et al. [54] (2015) of 23 papers found health-related quality of life was lower in subjects with CLP. Separate analyses were conducted for children, adolescents and adults. Emotional and functional well-

being were the most influential dimensions for children and adolescents for oral health-related quality of life and for physical, social and psychological dimensions of health-related quality of life. For adults, vitality was the dimension with the most impact for health-related quality of life. The authors noted a number of methodological differences between studies.

In 2013, a small cross-sectional study [55] reported that children with orofacial clefts had lower oral health-related quality of life and functional well-being and social-emotional well-being than children without these defects. They also found that social-emotional well-being was less among 15–18-year-old children than in younger ones.

Sischo et al. [56] (2017) in a critical review found that quality of life of both caregivers and affected individuals depends on the life stage at which the quality of life is assessed and the context in which they were placed. The quality of the surgical repair received may also influence quality of life [1]. Surgery also affected oral health-related quality of life. Surgery significantly improves functional and emotional well-being, self-esteem and general quality of life although the findings were not significant among their caregivers. A study of body image [57] found that among children with orofacial clefts, better oral health-related quality of life was associated with being male, being younger than 12 years and with having private insurance compared with being female, being older than 2 years and having no private insurance.

9.7.1 Health Outcomes

Wells [58] (2014) in review and meta-analysis found children with CLP have more caries in both permanent and deciduous dentitions than children without clefts as measured by the dmft/DMTF indices.

Hearing loss has also been found more commonly in CLP and CPO children. Skuladottir et al. [59] (2015) in a longitudinal study found that hearing loss was related to otitis media and that hearing improved as the child moved from childhood to adolescence. Kuo et al. [60] (2013) in a narrative review reported that about 90% of children with CLP will experience otitis media with effusion in the first year of life compared to 60% of non-affected children but that over 90% of children with CLP will have some conductive hearing loss compared to 13% of children without CLP. There is debate about the best approach to treatment of otitis media and associated hearing loss in CLP children [61].

Not only are OFC the most common craniofacial birth defects, they have also been linked with a higher risk of cancer in later life and an increased overall mortality well into adulthood [62, 63].

Thus, the impact of OFC is considerable on the child, stigmatises the family and is costly to the society in terms of health care and social exclusion and employment [64].

9.8 Conclusion

Orofacial clefts are a common birth defect which occurs in approximately 1 in 700 births. However, the frequency of such defects varies internationally and ethnically and in relation to SES. The development of the IPDTOC has been a major step forward. However, many countries particularly in Africa and Asia do not have national registries to contribute. Inequalities in prevalence, treatment and outcome exist between countries and within countries [64].

In developing countries, orofacial clefts result in high levels of disadvantage even infant mortality due to malnutrition or aspiration of milk. The availability, adequacy and the cost of effective treatment are major issues. In developed countries, affordability may also be an issue.

Preventive approaches to orofacial clefts require good evidence. As yet the evidence is mixed except for maternal smoking. Strong policies aimed at reducing smoking have been implemented in many developed countries but less so in developing countries. The effect of new forms of smoking has yet to be assessed. Behavioural modification in relation to dietary factors, use of particular medicines and other environmental factors may be possible in the future with further research.

Information from genetic studies on genes, gene-environmental interaction and interactions between genes continues to grow. In the future this may assist with genetic counselling for prospective parents.

Future research on possible preventive interventions, effective genetic screening and counselling [64] and ways to reduce the social impact are necessary. Social inequality in relation to availability, adequacy and affordability of treatment of orofacial clefts needs to be addressed as a priority.

References

1. Mossey PA, Little J, Munger RG, et al. Cleft lip and palate. Lancet. 2009;374(9703):1773–85.
2. IPDTOC Working Group. Prevalence at birth of cleft lip with or without cleft palate: data from the International Perinatal Database of Typical Oral Clefts (IPDTOC). Cleft Palate Craniofac J. 2011;48(1):66–81.
3. Fan D, Wu S, Liu L, et al. Prevalence of non-syndromic orofacial clefts: based on 15,094,978 Chinese perinatal infants. Oncotarget. 2018;9(17):13981–90.

4. Wang M, Yuan Y, Wang Z, et al. Prevalence of orofacial clefts among live births in China: a systematic review and meta-analysis. Birth Defects Res. 2017;109(13):1011–9.
5. Balaji SM. Burden of orofacial clefting in India 2016: a global burden of disease approach. Ann Maxillofac Surg. 2018;8(1): 91–100.
6. Marengo LK, Flood TJ, Ethen MK, et al; National Birth Defects Prevention Network. Study of selected birth defects among American Indian/Alaska Native population: a multi-state population-based retrospective study, 1999–2007. Birth Defects Res. 2018;110(19):1412–8.
7. Thompson JM, Stone PR, Sanders M, et al. The incidence of Orofacial Cleft in live births in New Zealand. N Z Med J. 2016;129(1440):Abstract.
8. Niswander JD, MacLean CJ, Chung CS, et al. Sex ratio and cleft lip with or without cleft palate. Lancet. 1972;2(7782):858–60.
9. Carinci F, Scapoli L, Palmieri A, et al. Human genetic factors in nonsyndromic cleft lip and palate: an update. lnt J of Pediatric Otorhinolaryngology. 2007;71:1509–19.
10. Little J, Cardy A, Munger RG. Tobacco smoking and oral clefts: a meta-analysis. Bull World Health Organ. 2004;82(3):213–8.
11. Kummet CM, Moreno LM, Wilcox AJ, et al. Passive smoke exposure as a risk factor for oral clefts-A large international population-based study. Am J Epidemiol. 2016;183(9):834–41.
12. Xuan Z, Zhongpeng Y, Yanjun G, et al. Maternal active smoking and risk of oral clefts: a meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(6):680–90.
13. Shi M, Wehby GL, Murray JC. Review on genetic variants and maternal smoking in the etiology of oral clefts and other birth defects. Birth Defects Res C Embryo Today. 2008;84(1):16–29.
14. Wehby GL, Uribe LM, Wilcox AJ, et al. Interaction between smoking and body mass index and risk of oral clefts. Ann Epidemiol. 2017;27(2):103–7.
15. Raut JR, Simeone RM, Tinker SC, et al; National Birth Defects Prevention Study. Proportion of orofacial clefts attributable to recognized risk factors. Cleft Palate Craniofac J. 2019;56(2); 151–9.
16. Sabbagh HJ, Hassan MH, Innes NP, et al. Passive smoking in the etiology of non-syndromic orofacial clefts: a systematic review and meta-analysis. PLoS One. 2015;10(3):e0116963.
17. DeRoo LA, Wilcox AJ, Lie RT, et al. Maternal alcohol binge-drinking in the first trimester and the risk of orofacial clefts in offspring: a large population-based pooling study. Eur J Epidemiol. 2016;31(10):1021–34.
18. Molina-Solana R, Yáñez-Vico RM, Iglesias-Linares A, et al. Current concepts on the effect of environmental factors on cleft lip and palate. Int J Oral Maxillofac Surg. 2013;42(2):177–84.
19. Xu DP, Qu WD, Sun C, et al. Study on environmental factors for nonsyndromic cleft lip and/or palate. J Craniofac Surg. 2018;29(2):364–7.
20. Bell JC, Raynes-Greenow C, Turner RM, et al. Maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol. 2014;28(4):322–32.
21. Romitti PA, Sun L, Honein MA, et al. Maternal periconceptional alcohol consumption and risk for orofacial clefts. Am J Epidemiol. 2007;134:298–303.
22. Bezerra JF, Oliveira GH, Soares CD, et al. Genetic and non-genetic factors that increase the risk of non-syndromic cleft lip and/or palate development. Oral Dis. 2015;21(3):393–9.
23. Ito K, Hanaoka T, Tamura N, et al. Association between maternal serum folate concentrations in the first trimester and the risk of birth defects: The Hokkaido Study of Environment and Children's Health. J Epidemiol. 2019;29(4):164–71.
24. Van Rooij IA, Ocké MC, Straatman H, et al. Periconceptional folate intake by supplement and food reduces the risk of nonsyndromic cleft lip with or without cleft palate. Prev Med. 2004;39:689–94.
25. Wilcox AJ, Lie RT, Solvoll K, et al. Folic acid supplements and risk of facial clefts: national population based case-control study. BMJ. 2007;334(7591):464.
26. Butali A, Little J, Chevrier C, et al. Folic acid supplementation use and the MTHFR C677T polymorphism in orofacial clefts etiology: an individual participant data pooled-analysis. Birth Defects Res A Clin Mol Teratol. 2013;97(8):509–14.
27. Millacura N, Pardo R, Cifuentes L, et al. Effects of folic acid fortification on orofacial clefts prevalence: a meta-analysis. Public Health Nutr. 2017;20(12):2260–8.
28. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, et al. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2015;(12):CD007950.
29. Johnson CY, Little J. Folate intake, markers of folate status and oral clefts: is the evidence converging? Int J Epidemiol. 2008;37(5):1041–58.
30. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009;301(6):636–50.
31. Block SR, Watkins SM, Salemi JL, et al. Maternal pre-pregnancy body mass index and risk of selected birth defects: evidence of a dose-response relationship. Paediatr Perinat Epidemiol. 2013;27(6):521–31.
32. Kutbi H, Wehby GL, Moreno Uribe LM, et al. Maternal underweight and obesity and risk of orofacial clefts in a large international consortium of population-based studies. Int J Epidemiol. 2017;46(1):190–9.
33. Carmichael SL, Shaw GM, Yang W, et al. Maternal stressful life events and risks of birth defects. Epidemiology. 2007;18(3):356–61.
34. Goenjian HA, Chiu ES, Alexander ME, et al. Incidence of cleft pathology in Greater New Orleans before and after Hurricane Katrina. Cleft Palate Craniofac J. 2011;48(6):757–61.
35. Waller DK, Hashmi SS, Hoyt AT et al; National Birth Defects Prevention Study. Maternal report of fever from cold or flu during early pregnancy and the risk for noncardiac birth defects, National Birth Defects Prevention Study, 1997–2011. Birth Defects Res. 2018;110(4):342–51.
36. Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. Pediatrics. 2014;133(3):e674–88.
37. Howley MM, Feldkamp ML, Papadopoulos EA, et al; National Birth Defects Prevention Study. Maternal genitourinary infections and risk of birth defects in the National Birth Defects Prevention Study. Birth Defects Res. 2018;110(19):1443–54.
38. Holmes LB, Hernandez-Diaz S. Newer anticonvulsants: lamotrigine, topiramate and gabapentin. Birth Defects Res A Clin Mol Teratol. 2012;94(8):599–606.
39. Krapels IP, Zielhuis GA, Vroom F, et al. Periconceptional health and lifestyle factors of both parents affect the risk of live-born children with orofacial clefts. Birth Defects Res A Clin Moleratol. 2006;76(8):613–20.
40. Carmichael SL, Nelson V, Shaw GM, et al. Socio-economic status and risk of conotruncal heart defects and orofacial clefts. Paediatr Perinat Epidemiol. 2003;17(3):264–71.
41. Clark JD, Mossey PA, Sharp L, Little J. Socioeconomic status and orofacial clefts in Scotland, 1989 to 1998. Cleft Palate Craniofac J. 2003;40(5):481–5.
42. Durning P, Chestnutt IG, Morgan MZ, et al. The relationship between orofacial clefts and material deprivation in Wales. Cleft Palate Craniofac J. 2007;44(2):203–7.
43. Lupo PJ, Danysh HE, Symanski E, et al. Neighbourhood-based socioeconomic position and risk of oral clefts among offspring. Am J Public Health. 2015;105(12):2518–25.

44. Pawluk MS, Campaña H, Rittler M, et al. Individual deprivation, regional deprivation, and risk for oral clefts in Argentina. Rev Panam Salud Publica. 2018;41:e110.
45. Figueiredo JC, Ly S, Magee KS, et al. Parental risk factors for oral clefts among Central Africans, Southeast Asians, and Central Americans. Birth Defects Res A Clin Mol Teratol. 2015;103(10):863–79.
46. Rahimov F, Jugessur A, Murray JC. Genetics of nonsyndromic orofacial clefts. Cleft Palate Craniofac J. 2012;49(1):733–91.
47. Grosen D, Chevrier C, Skytthe A, et al. A cohort study of recurrence patterns among more than 54,000 relatives of oral cleft cases in Denmark: support for the multifactorial threshold model of inheritance. J Med Genet. 2010;47(3):162–8.
48. Dixon MJ, Marazita ML, Beaty TH, et al. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet. 2011;12(3):167–78.
49. Leslie EJ, Marazita ML. Genetics of cleft lip and cleft palate. Am J Med Genet C Semin Med Genet. 2013;163C(4):246–58.
50. Zhu H, Kartiko S, Finnell RH. Importance of gene-environment interactions in the etiology of selected birth defects. Clin Genet. 2009;75(5):409–23.
51. Mossey PA, Little J, Steegers-Theunissen R, et al. Genetic interactions in nonsyndromic orofacial clefts in Europe-EUROCRAN study. Cleft Palate Craniofac J. 2017;54(6):623–30.
52. Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: Established teratogens and risk factors. Birth Defects Res A Clin Mol Teratol. 2015;103:652–5.
53. Stewart BT, Carlson L, Hatcher KW, et al. Estimate of unmet need for cleft lip and/or palate surgery in India. JAMA Facial Plast Surg. 2016;18:354–61 cited in Balaji SM. Burden of orofacial clefting in India 2016: a global burden of disease approach. Ann Maxillofac Surg. 2018;8(1): 91–100.
54. Corrêa de Queiroz Herkrath AP, Herkrath F, Bessa Rebelo MA, et al. Determinants of health-related and oral health-related quality of life in adults with orofacial clefts: a cross-sectional study. Cleft Palate Craniofac J. 2018;55(9):1244–57.
55. Ward JA, Vig KW, Firestone AR, et al. Oral health-related quality of life in children with orofacial clefts. Cleft Palate Craniofac J. 2013;50(2):174–81.
56. Sischo L, Wilson-Genderson M, Broder HL. Quality-of-life in children with orofacial clefts and caregiver well-being. Dent Res. 2017;96(13):1474–81.
57. Broder HL, Wilson-Genderson M, Sischo L. Health disparities among children with cleft. Am J Public Health. 2012;102(5): 828–30.
58. Wells M. Review suggests that cleft lip and palate patients have more caries. Evid Based Dent. 2014;15(3):79.
59. Skuladottir H, Sivertsen A, Assmus J, et al. Hearing outcomes in patients with cleft lip/palate. Cleft Palate Craniofac J. 2015;52(2):e23–31.
60. Kuo CL, Lien CF, Chu CH, et al. Otitis media with effusion in children with cleft lip and palate: a narrative review. Int J Pediatr Otorhinolaryngol. 2013;77(9):1403–9.
61. Tengroth B, Hederstierna C, Neovius E, et al. Hearing thresholds and ventilation tube treatment in children with unilateral cleft lip and palate. Int J Pediatr Otorhinolaryngol. 2017;97:102–8.
62. Bui AH, Ayub A, Ahmed MK, Taioli E, et al. Association between cleft lip and/or cleft palate and family history of cancer: a case-control study. Ann Plast Surg. 2018;80(4 Suppl 4): S178–81.
63. Setó-Salvia N, Stanier P. Genetics of cleft lip and/or cleft palate: association with other common anomalies. Eur J Med Genet. 2014;57(8):381–93.
64. Mossey PA, Shaw WC, Munger RG, et al. Global oral health inequalities: challenges in the prevention and management of orofacial clefts and potential solutions. Adv Dent Res. 2011;23(2):247–58.

Recommended Reading

Dixon MJ, Marazita ML, Beaty TH, et al. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet. 2011;12(3):167–78.

IPDTOC Working Group. Prevalence at birth of cleft lip with or without cleft palate: data from the International Perinatal Database of Typical Oral Clefts (IPDTOC). Cleft Palate Craniofac J. 2011;48(1):66–81.

Leslie EJ, Marazita ML. Genetics of cleft lip and cleft palate. Am J Med Genet C Semin Med Genet. 2013;163C(4): 246–58.

Molina-Solana R, Yáñez-Vico RM, Iglesias-Linares A, et al. Current concepts on the effect of environmental factors on cleft lip and palate. Int J Oral Maxillofac Surg. 2013;42(2):177–84.

Mossey PA, Little J, Munger RG, et al. Cleft lip and palate. Lancet. 2009;374(9703):1773–85.

Mossey PA, Shaw WC, Munger RG, et al. Global oral health inequalities: challenges in the prevention and management of orofacial clefts and potential solutions. Adv Dent Res. 2011;23(2):247–58.

Rahimov F, Jugessur A, Murray JC. Genetics of nonsyndromic orofacial clefts. Cleft Palate Craniofac J. 2012;49(1):733–91.

Enamel Defects

David J. Manton, Felicity Crombie, and Falk Schwendicke

Contents

10.1 Introduction – 170

10.2 Amelogenesis Imperfecta (AI) – 172
10.2.1 Prevalence of Amelogenesis Imperfecta – 172

10.3 Acquired DDE in the Primary Dentition – 173
10.3.1 Prevalence of DDE in Infants – 173
10.3.2 Factors Associated with Acquired DDE in Primary Teeth – 175
10.3.3 Hypomineralised Second Primary Molars – 176

10.4 Acquired DDE in Permanent Teeth – 176
10.4.1 Trauma – 177
10.4.2 Illness and Medication – 177
10.4.3 Molar–Incisor Hypomineralisation – 177

10.5 Summary – 184

References – 185

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_10

Learning Objectives

- To understand the several different types of DDE
- To have knowledge of the prevalence of DDE
- To understand the aetiological factors and pathogenesis of DDEs
- To have knowledge of the different indices used to quantify DDEs
- To be aware of the impact of DDE on caries experience, especially in the primary dentition

Conclusion

Developmental defects of enamel (DDE) affect a significant proportion of the population, with the possibility of defects in both primary and permanent dentitions. Two major defect types exist – hypoplasia and hypomineralisation (demarcated and diffuse lesions); and they can be hereditary (genetic) or acquired. The type of acquired defect depends on the timing of the aetiological factor's influence on the ameloblast – if it is during the secretion of transition phases or amelogenesis, then hypoplasia is more likely. Later, during the maturation phase, a hypomineralised defect is more likely.

Amelogenesis imperfecta is a hereditary condition with several phenotypes including hypoplastic and hypomineralised (hypocalcified and hypomature), with a prevalence ranging from 1 in 700 to 1 in 14,000, depending on the population.

Molar–incisor hypomineralisation (MIH) is a more recently recognised and defined acquired condition affecting permanent first molars and often incisors, which is likely to also have some genetic influences. The average worldwide prevalence of MIH is approximately 14%, with a huge range of close to zero to over 40%. At present, the aetiological factors are unknown, apart from a higher incidence amongst individuals who had infantile and childhood illnesses. All teeth in the primary and permanent dentitions can be affected with similar MIH-like demarcated lesions.

Overall, DDE show high prevalence. Early and correct diagnosis will aid correct treatment planning, improve the prognosis of affected teeth and maximise health outcomes in the affected individuals.

10.1 Introduction

Teeth have three distinct hard tissues – the enamel, dentine and cementum. Dental enamel is the hardest material in the human body, consisting of 96% mineral by weight, and 86% by volume [50]. Enamel acts as a resilient and hard layer covering the crown of the tooth, protecting the underlying softer, more bone-like dentine and the soft-tissue dental pulp.

The process of tooth formation is a highly controlled process; there are regulated signalling pathways that control cellular differentiation to form the developing tooth bud [14]. Amelogenesis involves two major phases for the ectodermally originated enamel forming cell, the ameloblast – matrix secretion followed by maturation, separated by the transitional phase [14, 107].

During the secretory phase, several matrix proteins are synthesised and secreted – namely amelogenin (AMELX), ameloblastin (AMBN) and enamelin (ENAM) [107, 176]. These proteins lay the foundation for future crystal growth, regulated by matrix metalloproteinases, especially MMP20. The amount of matrix secreted may be reduced, leading to thin, or hypoplastic, enamel. Some mineralisation occurs during the secretory stage; however, the vast majority is during maturation. The transitional phase is the period during which the ameloblast stops secreting matrix protein and upregulates genes involved in ion transport, pH regulation and proteolysis, in preparation for the maturation phase [107].

The maturation phase then involves the transport of ions, namely calcium and phosphate, into the developing enamel, secretion of proteases to enhance the increase in mineral density by the kallikrein-related peptidase 4 (KLK4)-assisted degradation of matrix proteins, pH regulation to assist mineral precipitation and cellular homeostasis, and endocytosis of remnant matrix proteins [14, 107]. After the completion of amelogenesis and complete mineralisation of the enamel, the ameloblasts undergo programmed apoptosis [165]. This complex tightly regulated process can be disrupted by environmental 'insults' and also variations in the genes associated with amelogenesis [107, 206]. As the ameloblasts are very active during amelogenesis, especially dealing with high concentrations of calcium and phosphate ions, they are easily 'upset'.

Therefore, developmental defects of enamel (DDE) can be caused by systemic, genetic, local and environmental aetiological factors affecting the quality and quantity of amelogenesis. Depending on when the ameloblast function is affected, if it is during secretion, the resultant defect manifests as a hypoplastic defect (quantitative defect) or, if the impact on the ameloblast is later during maturation, the lesion is a hypomineralised defect (qualitative defect) [207] (Fig. 10.1).

There is high prevalence of DDE in infants. Several authors have reported overall DDE prevalence values from 10% to 49% in the primary dentition [111, 157]. Primary teeth DDE that are not hereditary in nature are commonly acquired during the amelogenesis phase in a period that is before birth – and commonly related to maternal and foetal illness, including premature birth and low birth weight [31, 162].

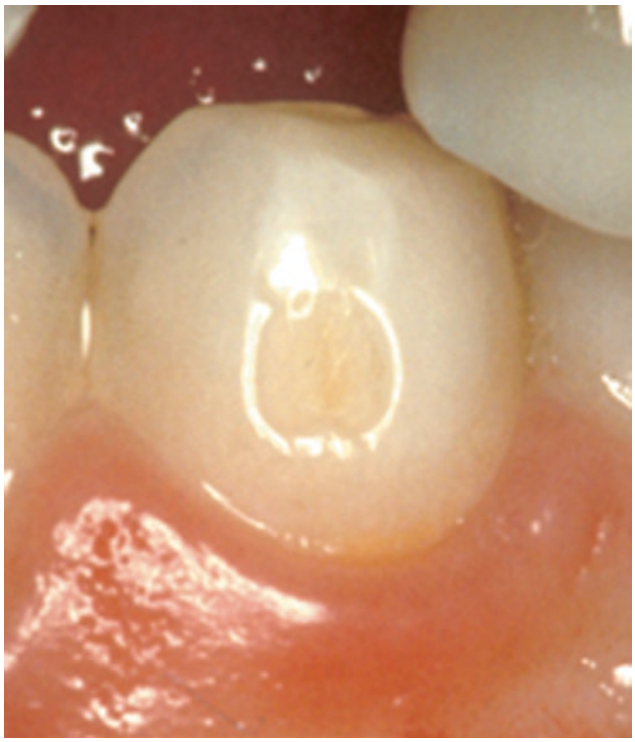


Fig. 10.1 Hypoplastic defect on mandibular primary canine

Table 10.1 Description criteria of modified DDE index

Code	
0	No visible enamel defect
	Demarcated Opacities
1	white/cream
2	yellow/brown
	Diffuse Opacities
3	Diffuse – Lines
4	Diffuse – Patchy
5	Diffuse – Confluent
6	Confluent/Patchy + staining + loss of enamel
	Hypoplasia
7	Pits
8	Missing enamel
9	Any other defects
	Extent of Defect
0	Normal
1	Less than 1/3
2	At least 1/3 and less than 2/3
3	At least 2/3

Clarkson and O'Mullane [27]

The most prevalently postulated putative systemic cause of DDE acquired after birth is childhood illness during amelogenesis, and only teeth forming during this period are affected, that is mostly permanent teeth, although there is a possibility that developing second primary molars may be damaged at the same time. Whether there is a direct genetic influence on the acquired defects is yet to be determined; however, a genetic influence is likely [174, 194].

DDE and, specifically, molar–incisor hypomineralisation (MIH) have garnered much interest in the past 20 years, with a perception that they are increasing in prevalence. Whether this is the case is open to discussion, however; in certain populations, caries experience has decreased, and therefore DDE are more readily diagnosed as they have not been destroyed by the caries process [174]. There is evidence of DDE and specifically MIH in ancient populations, indicating that they are not a 'new' phenomenon [61, 62].

Several indices have been used over the past 80 or so years to classify DDE – including fluorosis. The initial indices, including Dean's and the Tooth Surface Index of Fluorosis, were created for fluorosis [28]. It became apparent that other DDE existed (non-fluorotic), and so the FDI proposed the Developmental Defects of Enamel Index (DDE) in 1982 [53]. Subsequent to this, modifications were made to the original DDE index by Clarkson and O'Mullane to improve usability and 'to make the data recorded more amenable to analysis and interpretation' (Table 10.1) [27, 54].

Specific illness such as celiac disease and chronic kidney disease can increase the risk of DDE [116, 178]. A meta-analysis of studies regarding DDE in individuals with celiac disease indicates an increased risk of DDE (RR 2.31, 95% CI: 1.71–3.12) in those affected, with a mean prevalence of 50%, affecting both primary and permanent dentitions [178]. Hyperbilirubinaemia can cause green teeth; congenital porphyria can lead to deposition of reddish blood pigments in the teeth [207].

The most common (although rare) genetically based condition is amelogenesis imperfecta (AI) which has a variety of phenotypes [74]. Also, genetic influences have been postulated for MIH, with polymorphism identified in several genes associated with amelogenesis in affected individuals [184, 194].

Local causes of DDE are often traumatic in nature, such as those which come from physical trauma to a primary tooth (often an incisor) directly impacting on the developing permanent tooth bud and resulting in either a hypoplastic (more common) or hypomineralised DDE. Children who have had trauma to their primary teeth have increased prevalence of DDE in their permanent teeth [109].

10.2 Amelogenesis Imperfecta (AI)

AI is an encompassing term representing a heterogenous genetic and phenotypic group of inherited dental enamel defects [33]. AI affects all teeth, both primary and permanent of the affected individual, usually to a similar extent. The defects may be hypoplastic, hypomineralised (including hypocalcified and hypomature) or in some cases both defect types are present [33] (Fig. 10.2).

The enamel may be discoloured, and this can worsen with post-eruptive staining if there is difficulty with oral hygiene or the enamel is porous, or in hypoplastic cases, if the hypoplastic lesions are smaller than a toothbrush bristle and difficult to clean both at home and professionally.

The classification by Witkop in 1989, based on phenotype and mode of inheritance, has been used widely in the past 30 years (Table 10.2), although as the genetics of AI has become somewhat clearer, a new classification has been proposed by Aldred and colleagues, based on phenotype, mode of inheritance and, when known, the molecular defect and subsequent biochemistry [4, 204].

AI is linked with syndromes and also other conditions such as nephrocalcinosis, so a diagnosis of AI should engender some further thought regarding associated conditions [74–76].

Depending on the variant of AI, clinical implications vary considerably, from aesthetic concerns to rapid enamel breakdown, sensitivity and pain. Many individuals with AI require a lifetime of ongoing dental care due to the fragile nature of the enamel and difficulty in maintaining good oral hygiene due to sensitivity or roughness/irregularity of the tooth surface, which may also lead to inflammatory changes in the gingival tissues [74].

Table 10.2 Description criteria for Witkop's amelogenesis imperfecta index

Type of defect	Sub-classification
Type I Hypoplastic	IA – hypoplastic, pitted AD IB – hypoplastic, local AD IC – hypoplastic, local AR ID – hypoplastic, smooth AD IE – hypoplastic, smooth XLD IF – hypoplastic, rough AD IG – enamel agenesis, AR
Type II Hypomaturation	IIA – hypomaturation, pigmented AR IIB – hypomaturation, XLR IIC – hypomaturation, snow-capped XL IID – hypomaturation, snow-capped AD?
Type III Hypocalcified	IIIA – hypocalcified AD IIIB – hypocalcified AR
Type IV Hypomaturation–hypoplastic with taurodontism	IVA – Hypomaturation–hypoplastic with taurodontism AD IVB – Hypoplastic–hypomaturation with taurodontism AD

Witkop [204], Lacruz et al. [107]

10.2.1 Prevalence of Amelogenesis Imperfecta

Few larger studies exist regarding the prevalence of AI. In the classical studies of Witkop in Michigan, USA, prevalence ranged between 0.06 and 0.07:1000 (1:14,000–1:16,000) in 96,471 children [203]. In 70,359 Israeli children, a prevalence of 0.1:1000 (1:8,000) was reported [26]. Contrary to this finding, in a Swedish study of 56,663 children and adolescents, a prevalence of 1.4:1000 (1:717) was determined [11]. Although in a separate Swedish population-based study of 425,000 children undertaken around the same time, a prevalence of approximately 1:4000 was reported [183]. Potential reasons for the differences in the two Swedish studies remain unclear, and Bäckman and Holm postulate that their high Swedish prevalence values may be due to genetic differences in the region from where the children came from. Notably, in both studies, children were referred from public dentists, which comes with the potential for underestimation of prevalence.

In three more recent smaller clinic-based studies, 3 of 1123 participants (1:374) in an Indian population, 13 of 3043 Turkish children undergoing orthodontic treatment (1:234) and 4 of 1252 Saudi Arabian children (1:313) had AI [7, 71, 212]. Caution must be taken interpreting these data due to the small sample sizes and the possibility the sample may be biased due to the clinic-based nature of the studies.

Regarding AI type, in Bäckman and Holm's study, hypoplastic types comprised 73%, with 'hypomineralisation and hypomaturation' types making up the

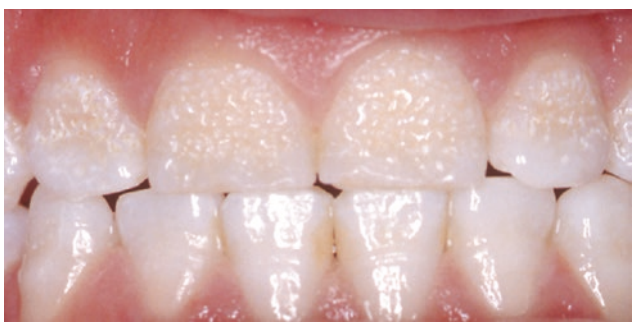


Fig. 10.2 Amelogenesis imperfecta – pitted hypoplastic

remainder. In Israel, a similar higher prevalence for hypoplasia was noted, different from the higher prevalence of hypomineralised types in Michigan children [11, 203].

10.3 Acquired DDE in the Primary Dentition

Two major acquired DDE exist – hypoplastic and hypomineralised lesions. Hypoplasia can occur as pits or linear (usually horizontal) defects. Hypomineralised lesions can be diffuse or demarcated. Demarcated lesions can be white, cream, yellow or brown in colour. Diffuse lesions tend to be white in colour, and, if mild, can be difficult to distinguish.

The potential impact of DDE on the primary dentition in infants is vastly different to that on permanent teeth due to several reasons – primarily age and associated behavioural characteristics, such as those associated with early childhood caries [170].

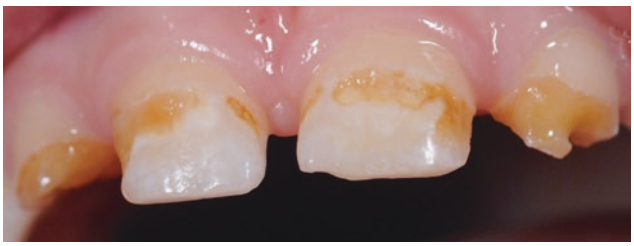
The presence of DDE increases the likelihood of carious lesion development [170]: in the case of hypoplastic enamel, by a physical niche on the tooth surface where biofilm can be protected from routine oral hygiene practices; or for hypomineralisation by the enamel lesion having already reduced mineral density, porous and rough surface and weak physical characteristics predisposed to dissolution and breakdown. Hypersensitivity of DDE teeth further impedes oral hygiene and increases the risk of caries development. As a result, infants with DDE have higher caries experience, with a risk increase of approximately two to three times reported [32, 64, 81, 157, 190]. It is likely that common risk factors (including maternal health during pregnancy, low socioeconomic status and others such as childhood illness and behavioural factors such as the parental ability to provide a healthy diet and clean the child's teeth) also play a role [56, 162] (◘ Fig. 10.3).

More recently, a specific definition of a hypomineralised defect – hypomineralised second primary molars (HSPM) – has been promulgated. This definition relates second primary molars being affected in a manner similar to the first permanent molars initially defined in molar–incisor hypomineralisation (MIH) [44, 45]. These will be discussed in more detail later in the text .

10.3.1 Prevalence of DDE in Infants

The prevalence of DDE in infants is often stated to range between 20% and 40%, although the range varies hugely (see ◘ Table 10.3) [112, 151, 162]. Individual societal and social contexts influence the prevalence and incidence of DDE in children. Therefore, knowing the context of individual studies is important before the results can be extrapolated broadly. Many studies are undertaken in populations within specific environments, backgrounds or having medical conditions, and therefore a lot of the data cannot be extrapolated to the general population.

Hypomineralisation appears to be the more prevalent DDE, with the predominance of either diffuse or demarcated hypomineralised lesions varying in the literature [81, 111, 114, 151] (◘ Fig. 10.4).



◘ **Fig. 10.3** Primary incisors with hypoplasia. (Courtesy Dr Michael Wyatt)

◘ **Table 10.3** Prevalence of developmental defects of enamel (DDE) of the primary dentition

Country	Authors	Age (years)	Sample size	DDE prevalence (%)	Enamel opacity prevalence (%)	Criteria (index) used
Australia	Seow et al. [166]	3.5–5.9	68	98	1.1 ± 0.8 affected teeth per child	DDE
Australia	Seow et al. [168]	6.3	163	25	15	mDDE
Australia	Seow et al. [170]	0–6	725	10.2		mDDE
Australia	Owen et al. [137]	3–5	623		14.1	EAPD
Australia	Gambetta et al. [58]	6–12	371		8	EAPD

(continued)

Table 10.3 (continued)

Country	Authors	Age (years)	Sample size	DDE prevalence (%)	Enamel opacity prevalence (%)	Criteria (index) used
Brazil	Lunardelli and Peres [114]	3–5	431	24.4	6.1	mDDE
Brazil	Chaves et al. [24]	1–3	275	78.9	3.1	DDE
Brazil	Se et al. [164]	6–11	1590		6.5	EAPD
Canada	Wang [197] unpubl		429		5.2	EAPD
Chile	Gambetta-Tessini et al. [59]	6–12	577		5	EAPD
China	Li et al. [112]	3–5	1344	23.9	1.6	mDDE
China	Li et al. [111]	3–6	1351	48.3 Inner city 54.1 Suburban 42		mDDE
England	Weeks et al. [198]	4–5	242	Fluoridated 35 Low Fluoride 20	7	(Only incisors were examined) mDDE
Germany	Kűhnisch et al. [102]	10	693		6.9	EAPD
Germany	Wagner [196]	3.3	377	5.3		mDDE
India	Kar et al. [93]	3–5	308		0	mDDE
India (Uttar Pradesh)	Mittal and Sharma [125]	6–8	978		5.6	EAPD
Iraq	Ghanim et al. [64]	7–9	823	–	6.6	EAPD
Mexico	Casanova-Rosado et al. [23]	6–12	1296	10		FDI
The Netherlands	Elfrink et al. [45]	5	386	–	4.9	EAPD
The Netherlands	Elfrink et al. [47]	5	62		21.8	EAPD
The Netherlands	Elfrink et al. [43]	6	6690		9.0	EAPD
Nigeria	Oyedale et al. [139]	8–10	469		5.8	EAPD
Central Saudi Arabia	Rugg Gunn et al. [153]	2, 4, 6	390 boys	43	12	DDE
Western Saudi Arabia	Farsi et al. [52]	4–5	510	45.4	2.4	mDDE
Singapore	Ng et al. [134]	7.7	1083		2.9	EAPD
Thailand	Kanchanakamol et al. [92]	1–4	344	31.9	9.3	Enamel hypoplasia index (EHI)
USA	Slayton et al. [175]	4–5	698	–	27	DDE
USA	Nation et al. [131]	3–6	300	33	12	Modified FDI
USA	Montero et al. [128]	3–5	517	49	–	mDDE

Alaluusua et al. [3], Cabral [21], Calderara et al. [22], Research & Epidemiology FDI Commission on Oral Health [53], Clarkson and O'Mullane [27], Weerheijm et al. [199], Kemoli [94], Koch et al. [98], Research & Epidemiology. Report of an FDI Working Group FDI Commission on Oral Health [54], Weerheijm et al. [200]

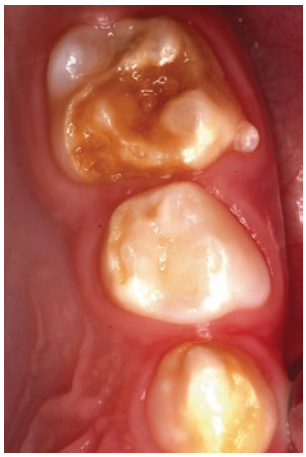


Fig. 10.4 Hypomineralised primary teeth. (Courtesy Dr Marilyn Owen)

At the higher end, Seow and colleagues reported a DDE prevalence of 98% in a small Australian Aboriginal population [166]; in a recent Chinese study (Shanghai; N = 1351), the prevalence of DDE was 48.3%, with prevalence higher in inner-city residing children compared to suburban children. Caries prevalence increased as DDE severity increased [111].

10.3.2 Factors Associated with Acquired DDE in Primary Teeth

Factors that have been associated with increased prevalence of DDE (including both hypoplastic and hypomineralised lesions) in infants include perinatal illness and medication of the child and mother during amelogenesis of the primary teeth.

Infants or newborns who have had laryngoscopy and/or intubation are at increased risk of DDE, especially in the anterior teeth due to direct trauma to the developing teeth via the mucosa and bone. In a study in Brisbane, Australia, there were DDE in 85% of intubated children compared to 21.7% of non-intubated [167].

Premature birth and low birth weight (LBW) also influence the prevalence of DDE, increasing the odds by 2.2–7.5 for pre-term infants [31, 162]. In a large retrospective study of 7518 children treated at the Royal Children's Hospital of Melbourne (RCH), 56.5% of 765 premature children had DDE [73]. The prevalence of DDE increases with decreasing birth weight; for example 14 of 16 children (87.5%) born lighter than 1000 g had DDE compared to 37 of 47 (78.7%) born heavier (1000–1500 g) [167]. Similarly, in a further study, Seow and colleagues report 48 of 77 (62.3%) of children born with very low birth weight (VLBW; <1500 g) had DDE; compared to 9 of 33 (27.3%) with LBW (1500–2500 g) and 6 of 47 (12.8%) with normal birth weight (>2500 g) [169]. And in a later Brisbane study, 96% of 25 children with VLBW had DDE at 52 months of age, compared to 45% of children with normal BW [108].

In the Brazilian context, DDE in children born preterm (PT) had higher prevalence compared to full-term (FT) birth: for PT children – opacity 18.8%, hypoplasia 37.5%, compared to FT children – opacity 28.1%, hypoplasia 8.3%. Interestingly, the prevalence of hypoplasia was predominant in PT and the opposite for FT. In the PT group of children who were given parenterally delivered nutrition, 12.3% had opacities and 56.1% had hypoplasia, showing little influence of the nutritional source. In the PT children with VLBW, 13 of 70 (18.6%) and 36 of 70 (51.4%) of children had enamel opacities and hypoplasia, respectively; in LBW children, 3 of 19 (15.8%) had opacities and no children had hypoplasia; in children with normal BW, 2 of 7 (28.6%) had opacities, and like LBW children, none had hypoplasia [69]. Similar results were reported in a smaller Brazilian study, with an overall DDE prevalence of 46.3%, and increased odds of DDE in PT or very PT children (RR 2.2), VLBW (RR 2.0), neonatal intensive care ward admission (RR 1.3) and perinatal intubation (RR 1.6) [31].

The age at examination can influence prevalence data due to the eruption dates of primary teeth. In a US study of 468 children, at 8 months the distribution for VLBW (n = 149) was 18.8% hypoplasia, 8.1% demarcated, 24.8% overall; for NBW (n = 149) it was 2.0% hypoplasia, 5.4% demarcated, 8.1% overall, whereas at 18 months, the distribution for VLBW (n = 194) was 30.9% hypoplasia, 19.6% demarcated, 43.8% overall; for NBW (n = 184) it was 8.2% hypoplasia; 15.8% demarcated; 24.5% overall [133].

In a recent German study of 377 3-year-old children, a relatively low DDE prevalence of 5.3% was reported. The second primary molars were most affected and demarcated opacities most prevalent. Despite the relatively low prevalence, in support of the previously mentioned studies, DDE were associated with preterm birth (OR 4.9) and hospitalisation in first year of life (OR 4.6) [196]. In a smaller recent German study (N = 128), higher OR were reported for DDE in PT infants (OR 7.5), with increased number of surfaces affected by DDE as the birth weight decreased. In PT children, hypomineralisation was more prevalent than hypoplasia, with the opposite in FT children [162].

Infant disease can also increase DDE prevalence. In an Australian study, 81.8% of 771 children with rubella embryopathy had DDE, compared to 9.3% in the control group of 893 children with only dental disease [73]. Around one-quarter of children with cleft lip and palate (27.9%), and cleft lip and alveolus (26.4%) had DDE,

although the author claimed this was lower than reality due to incomplete record keeping early in the study. A prevalence of 23.6% and 21.5% of children with metabolic disorders (mainly celiac disease) and dermatologic disorders with DDE, respectively, existed [73].

Medication during pregnancy may also increase DDE prevalence. For example, antiepileptic drugs taken during pregnancy increased DDE in the primary dentition – Hypoplasia – 11% vs control 4%; Diffuse 18% AED vs 7% control; white opacities 18% AED vs 10% control [85]. Although results from a large Dutch study indicated that anti-asthma, anti-allergy and antimicrobial drugs taken during pregnancy did not increase the prevalence of DDE in the offspring [43].

10.3.3 Hypomineralised Second Primary Molars

HSPM has been defined as a specific entity in children, borrowing from the definition of MIH. It is a demarcated hypomineralised defect of enamel affecting a second primary molar – often associated with MIH. It is a subset of DDE in primary teeth [45, 64].

Several studies have correlated HSPM with a higher risk of developing MIH. This is not unexpected as there is overlap in the developmental periods of the first permanent molars and second primary molars. The increased risk of MIH when HSPM is present has been cited as being between 1.5 and 4.8 times higher [42, 64, 127]. In an Indian study of over 1100 children, 48% of those with MIH also had HSPM [127]. However, in two recent studies, the risk of MIH in children with HSPM was 6.3 times (95% CI 3.03–15.35) and 7.82 times (95% CI 4.18–14.65) higher than in children without HSPM [125, 164]. An association between the presence of hypomineralised primary canines and MIH (OR 6.02; 95% CI 1.46–24.75) has also been reported [164]. Therefore, clinically, the presence of HSPM should indicate to the clinician that anticipatory guidance should be given to the parents regarding the increased chance of MIH, and the importance of early diagnosis of MIH reinforced.

10.4 Acquired DDE in Permanent Teeth

As acquired DDE can also include fluorosis, which is covered elsewhere, we will exclude fluorotic DDE here. The prevalence of acquired DDEs in the permanent dentition varies considerably between studied populations, just as in the primary dentition. Reported prevalence ranges from approximately 20% to above 90%, with comparability of data from the studies being limited due to defect indices used and participant variables such as socio-economic status and maternal–child illness [80, 96, 117, 151, 188, 189]. Similarly, there is a considerable difference in the prevalence of DDEs in permanent teeth between healthy children and those with systemic disease.

Hypoplasia tends to be less prevalent in the permanent than in the primary dentition. In a recent cross-sectional study of 1206 Brazilian schoolchildren, there was an overall DDE prevalence of 64%, consisting of diffuse opacities 35%, demarcated opacities 29.5% and hypoplasia 3.7% [189]. These results were similar to those reported in a Malaysian study, with 56% overall prevalence, and large differences in DDE between fluoridated and non-fluoridated water areas, with 21.5% and 67.4% demarcated and diffuse opacity prevalence in the fluoridated areas compared to 6.4% and 35.8% in non-fluoridated, respectively. Hypoplasia was more prevalent in the fluoridated areas (7.5% vs 3.1%,) [135]. In a recent study of 796 Swedish adolescents, the overall prevalence was 33.2%, consisting of 18.1% demarcated opacities (12.2% classified as MIH), 5% diffuse opacities and 1% hypoplasia [87]. Reporting a similar range in 945 children in Jena, Germany, Willing and colleagues determined overall DDE prevalence of 40.7%, with 27% demarcated and 21.1% diffuse lesions, and 2.4% hypoplasia [202]. The low prevalence of hypoplastic defects in permanent teeth was also present in a New Zealand study, with overall DDE prevalence 51.6%, demarcated 38.8%, diffuse opacities 24.1% and hypoplasia 5.5%, with diffuse opacities more prevalent in fluoridated regions (OR 2.23; 95% CI 1.37–3.63) [117]. Variable DDE and hypoplasia prevalence values are also present in Iraqi (DDE: 23.9%; Hypoplasia: 5.6%) and Iranian (DDE: 38.1%; Hypoplasia: 10.9%) studies [63, 66].

Interestingly, enamel hypoplasia has been used by anthropologists for decades as an indicator of illness or nutritional deprivation in ancient populations. Specifically, linear enamel hypoplasia (LEH) is most commonly used as an indicator of the age of the child when affected by the causative factor (insult) [186]. The periodicity of the LEH indicates the period between the insults to the secretory phase ameloblasts. Prevalence of LEH in ancient populations, like present populations, varies considerably. In a review of North American studies of populations living from 950 to 1300 A.D., the prevalence of LEH ranged from 45% to 80% [68]. Reliability and validity issues for using LEH in ancient populations include tooth wear, which confounds estimation of the developmental period of the affected enamel. The hypomineralised defect of enamel as an indicator of ameloblast stress (during the maturation phase) has not been widely recognised in anthro-

pological studies; more recently, researchers have recognised that hypomineralised defects do exist in these populations, although a population-level prevalence value has not been determined due to relatively small numbers [61, 62, 122]. In a study of the remains of 225 individuals from three regions in Germany in the twelfth to twentieth centuries, approximately 30% had LEH (similar in each region) and 18.3% had diffuse hypomineralisation. Regarding MIH, 10 of 323 (3.1%) individuals had signs of MIH [103]. Demarcated opacities in teeth from gravesites can be confounded by taphonomic stain, which appear, in many cases, similar to MIH lesions [62, 122]. The stain originates from elements in the soils (such as iron and manganese) in which the teeth have laid, although methods have been developed recently to distinguish between the lesion types [62].

10.4.1 Trauma

Direct trauma to the developing permanent tooth bud, such as that seen after trauma to or infection of the primary teeth, can also cause defects of enamel.

Children who have had trauma to their primary teeth have increased prevalence of DDE in their permanent teeth [109]. This is mostly confined to the permanent anterior teeth rather than the premolars due to their position with respect to likely traumatic incidents [109]. Premolars can be affected as well due to infection of the pulpal tissue of primary molars leading to periapical inflammation and subsequent DDE (Turner's hypoplasia). The more severe the traumatic episode or infection, the greater the likelihood of increased severity of the DDE [109].

Permanent DDE are increased in prevalence in individuals with cleft lip and palate (CL&P), with a potential cause of trauma being reparative surgery, especially in children who receive an early primary alveolar bone graft around 1–2 years of age [5, 154]. The process of clefting has also been proposed as a joint cause of the increased prevalence of DDE, potentially due to interrupted blood supply to the area, affecting metabolic processes such as amelogenesis [73].

In CL&P children, DDE are mainly present in the anterior maxillary teeth [1]. In a Brazilian study, 74 of 80 patients had DDE, with 50.7% being hypoplastic in nature, with diffuse and demarcated opacities being less prevalent (23.1% and 18.4%, respectively) [154]. Allam and colleagues investigated DDE (MIH) in CL&P patients and reported significantly higher prevalence in individuals with CL&P (36/41; 88%) compared to unaffected individuals (14/60; 23%) [5]. Interestingly, they did not detect any demarcated lesions in the mandibular index teeth. The pathogenesis being putatively related to the presence of cleft and also bone grafting that is commonly undertaken in these individuals.

10.4.2 Illness and Medication

The relationship between illness during amelogenesis and DDE in permanent teeth has been well documented over many decades. Numerous diseases and syndromes have been associated with increased prevalence of DDE in the permanent dentition, including mumps, celiac disease, chronic kidney disease, vitamin D-dependent rickets, tricho-dento-osseous syndrome, Noonan syndrome, epidermolysis bullosa, sickle cell anaemia, tuberous sclerosis, acute renal disease, tuberculosis, cholera, HIV, and endocrine disorders such as thyroid and pituitary disturbances [77, 116, 207].

However, the magnitude of any such association remains unclear. For example the range of DDE in those with celiac disease was reported to be 10–96% [116]. A meta-analysis of studies regarding DDE in individuals with celiac disease indicates an increased risk of DDE (RR 2.31, 95% CI:1.71–3.12) in those affected, with a mean prevalence of 50%, affecting both primary and permanent dentitions [178]. Like in the primary dentition, medication taken during pregnancy can also increase DDE prevalence. For example antiepileptic drugs taken during pregnancy increased DDE in the permanent dentition, with an increased risk of numerous (>3) white opacities (34% vs 12%, OR = 3.3) [85].

10.4.3 Molar–Incisor Hypomineralisation

MIH is, more recently, one of the most researched acquired enamel defects since its definition close to 20 years ago. MIH is a distinct definition of at least one permanent first molar having a demarcated hypomineralised enamel lesion present; frequently permanent incisors are also affected [199, 201]. After the definition of MIH in the early 2000's, it was realised that a more specific index would be beneficial for identifying, classifying and quantifying MIH. Following from Koch and colleagues' earlier research, the expert working group considered there were five important factors to record:

- Absence or presence of demarcated opacities
- Post-eruptive enamel breakdown (PEB)
- Atypical restorations
- Extraction of molars due to MIH
- Failure of eruption of a molar or an incisor [98, 199]

This led to the development of the EAPD MIH index; there is also a training manual available now for the use

Table 10.4 Description criteria of EAPD MIH index

Clinical status criteria (short form)
0 = No visible enamel defect 1 = Enamel defect, not MIH/HSPM 2 = White, creamy demarcated, yellow or brown demarcated opacities 3 = Post-eruptive enamel breakdown (PEB) 4 = Atypical restoration 5 = Atypical caries 6 = Missing due to MIH/HSPM 7 = Cannot be scored
Clinical status criteria (long form)
0 = No visible enamel defect 1 = Enamel defect, not MIH/HSPM 11 = diffuse opacity 12 = hypoplasia 13 = Amelogenesis Imperfecta 14 = hypomineralisation defect (not MIH/HSPM) 2 = Demarcated opacities 21 = White or creamy demarcated opacities 22 = yellow or brown demarcated opacities 3 = Post-eruptive enamel breakdown (PEB) 4 = Atypical restoration 5 = Atypical caries 6 = Missing due to MIH/HSPM 7 = Cannot be scored[a]
Lesion extension criteria (Index teeth only, scores 2–6)
I = less than one third of the tooth affected II = at least one third but less than two thirds of the tooth affected III = at least two thirds of the tooth affected
Modified after Ghanim et al. [67] [a]Tooth with extensive coronal breakdown and where the potential cause of breakdown is impossible to determine

of this index [65, 67, 199]. Although the EAPD index is the most commonly used, allowing for comparison between studies, it is not the only index promoted for use with MIH surveys, as can be seen in Table 10.4. There is heterogeneity in the phenotype of MIH – from a small lesion on one molar to all index teeth being affected, with severity of lesions varying not only between teeth but also within teeth. Lesions vary in colour, with darker lesions tending to be more severe (Fig. 10.5).

As colour of the lesion moves from the more prevalent white via yellow to the less prevalent brown, the severity of mineral deficit increases and clinical consequences are more severe [36, 63]. The lesions rarely (if ever) occur in the cervical third of the tooth. Variability is a major feature of MIH, and creates specific challenges in management for the clinician, as well as for the determination of the aetiological factors and pathogenesis. Putative aetiological factors have centred around childhood illness; however, as yet, no specific factors have been identified. This would indicate that there is some variability in individual susceptibility to developing MIH, most likely with some genetic influences [20, 191–195].

There is also regional variability (Table 10.5) of MIH prevalence, for example in India varying from 0.5% to 21.4%. This may be due to true regional differences, index used, validity of data collection and analysis, or non-representative samples. Vieira has postulated that the regional variation in prevalence may be an illustration of genetic influence on MIH, highlighting the relatively low prevalence in Egypt and comparing it to higher European values [193] (Fig. 10.6).

Some of the initial research into idiopathic enamel hypomineralisation (now known as MIH) identified variability in prevalence between different birth cohorts [98]. In this Swedish study ($N = 2252$), children born in 1970 had considerably higher prevalence of the defects compared to the birth years either side of 1970. This led to speculation regarding specific causative factors; however, to this day the aetiology of MIH is still unclear [34, 174].

As with DDE in primary teeth, there is a link between MIH and increased prevalence and severity of dental caries. This relationship has been reported in many studies from diverse settings worldwide [9, 59, 102, 159]. A systematic review of 17 studies of the link between MIH and dental caries determined children with MIH had an increased risk of between 2.1 and 4.6 times to develop dental caries [8]. An earlier systematic review of nine papers determined an OR of 2.21 [190] (Fig. 10.7).

As the recognition of MIH has increased globally and data from most continents have become available, the impact of its presence is becoming apparent [214]. In a recent meta-analysis of 99 studies with 113,144 participants from 43 countries, a mean prevalence of 13.1% (11.8–14.5%) was determined. The resultant number of prevalent cases estimated was 878 (791–971) million people, whilst the incident number of cases was 17.5 (15.8–19.4) million. An estimation of treatment need due to sensitivity, pain or post-eruptive enamel breakdown was 240 million prevalent and 4.8 million incident cases [163] (Fig. 10.8).

The limitation of this information is that little prevalence data are available from North America; however, recent Canadian data from the Sick Kids Hospital in Toronto indicated an MIH prevalence of 12.4% ($N = 429$), although these data should be interpreted with caution as DDE prevalence in children attending hospitals may not be representative of the general popu-

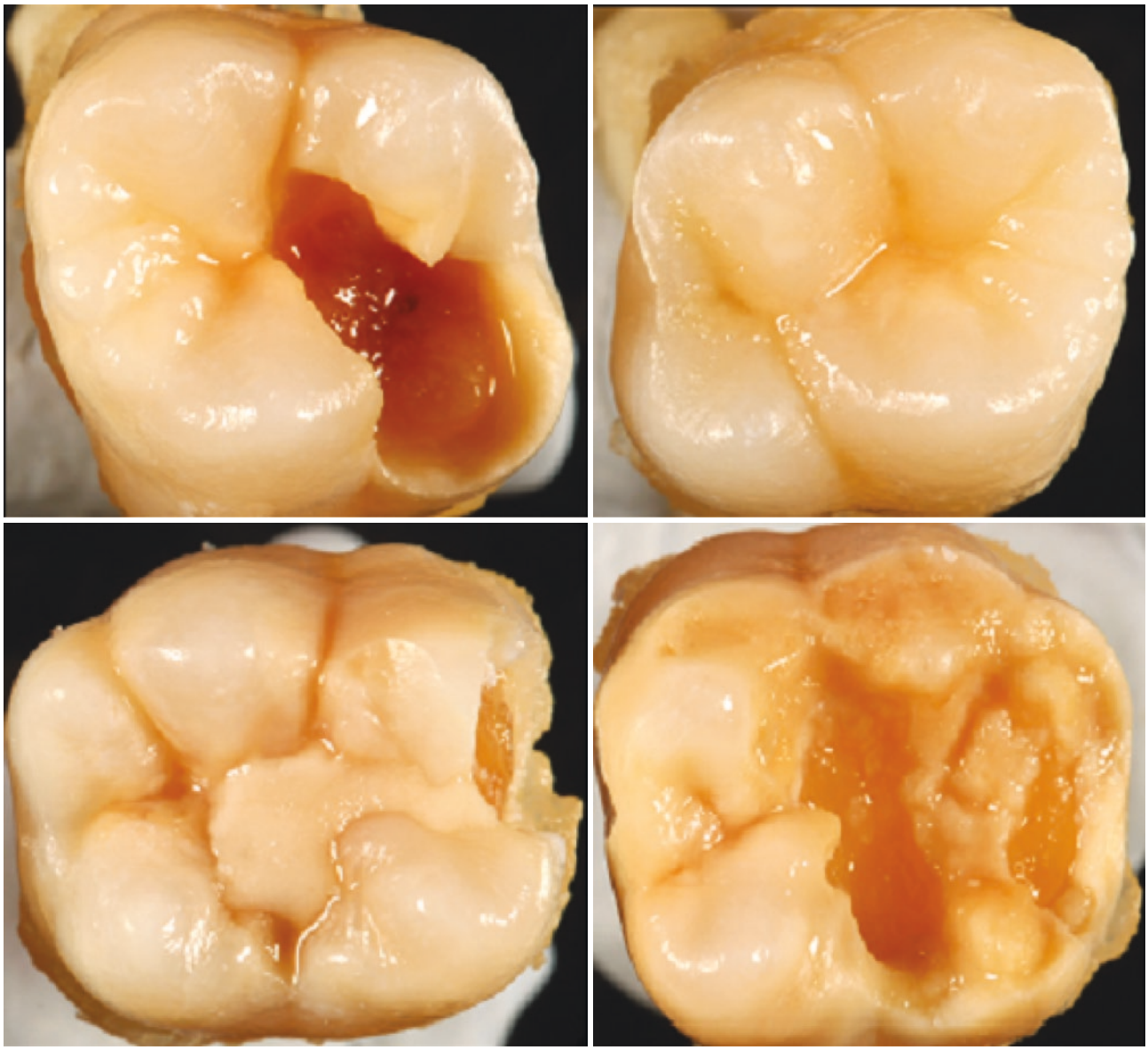


Fig. 10.5 MIH – first permanent molars from same individual. (Courtesy Dr Harleen Kumar)

lation, due to the potential confounding effect on prevalence of childhood illness [197].

The estimated cost of this treatment need would depend on the local treatment environment; however, for children (which is when most of the treatment need arises), it is not an inconsiderable proportion of treatment need [86, 110].

The main reason for the resultant treatment needs of individuals with MIH is the changes in physical and visual characteristics and associated discomfort. There is decreased mineral density of enamel, leaving it softer, less fracture resistant, more soluble, with a higher carbonate content, higher ionic substitution in the hydroxyapatite crystals, increased protein content and change in appearance [35, 48, 49, 51, 149].

In MIH a pattern of presentation exists in which the higher the number of teeth affected, the higher the chance of increased severity of the defects. As severity increases, normally with an increase in lesion colour (white to yellow to brown), so does the risk of post-eruptive breakdown, associated carious lesions and discomfort [136, 142, 149]. Interestingly, the permanent incisors are less severely affected compared to the first permanent molars, and the buccal surfaces of the incisors are more prevalently affected than any other surface – the reason for this can only be speculated upon.

All teeth can be affected by lesions similar to those in MIH, both primary and permanent dentitions – although the MIH distribution pattern is most prevalent [102].

Table 10.5 Prevalence of molar–incisor hypomineralisation and demarcated opacities worldwide

Country	Authors	Age (years)	Sample Size	Defect prevalence (%)	Criteria
Albania	Hysi et al. [84]	8–10	1575	14	EAPD
Argentina	Biondi et al. [16]	11.3	1098	15.9	DDE
Argentina	Biondi et al. [17]	11.6	512	6.4	Weerheijm [200]
Argentina	López Jordi et al. [113]	7–17	1090	16.1	Weerheijm [200, 201]
Australia	Balmer et al. [13]	8–16	25	44	mDDE
Australia	Arrow [10]	7.1	634	22 (demarcated)	mDDE
Australia	Gambetta et al. [58]	6–12	327	14.7	EAPD
Austria	Buchgraber et al. [19]	6–12	1111	7	EAPD
Bosnia-Herzegovina	Muratbegovic et al. [130]	12	560	12.3	EAPD
Bosnia-Herzegovina	Jankovic et al. [88]	8	141	12.8	EAPD
Bosnia-Herzegovina	Mulic et al. [129]	8–9	103	11.7	EAPD
Brazil	Soviero et al. [181]	7–13	249	40.2	EAPD
Brazil	da Costa-Silva et al. [37]	6–12	918	19.8	EAPD
Brazil	Souza et al. [179]	6–12	903	19.8 (rural 24.9, urban 17.8)	EAPD
Brazil	Jeremias et al. [91]	6–12	1157	12.3	EAPD
Brazil	Souza et al. [180]	7–12	1151	12.3	EAPD
Brazil	Silva Junior et al. [173]	5–17	260	8.8	EAPD
Brazil	De Lima et al. [40]	11–14	594	18.4	EAPD
Brazil	Rodrigues et al. [152]	7–14	1179	2.5	mDDE
Brazil	Tourino et al. [187]	8–9	1181	20.4	EAPD
Brazil	da Costa-Silva et al. [38]	5–6	142	16.2	
Brazil	Se et al. [164]	6–11	858	14.7	EAPD
Brazil	Dantas-Neta et al. [39]	8–10	744	25	EAPD
Brazil	Raposo et al. [149]	8	631	16.1	Cabral
Brazil	Vargas-Ferreira et al. [189]	8–12	1206	26.4 all teeth	mDDE
Brazil	Portella et al. [145]	8	728	12.1	EAPD
Bulgaria	Kukleva et al. [104]	7–14	2960	3.6 (2.4–7.8)	EAPD
Canada	Wang et al. [197] (unpubl)	0–17	233	12.4	EAPD
Chile	Gambetta et al. [59]	6–12	577	15.8	EAPD
China (Hong Kong)	Cho et al. [25]	11–14	2635	2.8	EAPD
Denmark	Wogelius et al. [205]	6–8	745	37.3	EAPD
Egypt	Saber et al. [155]	8–12	1001	2.3	EAPD

Table 10.5 (continued)

Country	Authors	Age (years)	Sample Size	Defect prevalence (%)	Criteria
Finland	Alaluusua et al. [3]	6–7	102	17	Alaluusua
Finland	Leppaniemi et al. [110]	7–13	488	19.3	Alaluusua
Finland	Wuollet et al. [209]	7–13	818	17.1 (rural 11.5, urban 21.3)	EAPD
Finland	Wuollet et al. [210]	7–12	287	11.5	EAPD
Finland	Wuollet et al. [208]	8–13	636	18.1	EAPD
Germany	Dietrich et al. [41]	10–17	2408	5.6	Jalevik [86]
Germany	Willing et al. [202] Abstract	6–12	945	27	mDDE
Germany	Preusser et al. [147]	6–12	1002	5.9	Koch et al. [98]
Germany	Heitmuller et al. [78]	10	693	14.7	EAPD
Germany	Kohlboeck et al. [99]	10	1126	13.7	EAPD
Germany	Kühnisch et al. [102]	10	693	14.7	EAPD
Germany	Petrou et al. [143]	8.1	2395	10.1	EAPD
Great Britain	Balmer et al. [13]	8–16	25	40	mDDE
Great Britain	Balmer et al. [12]	12	3233	15.9	mDDE
Greece	Lygidakis et al. [115]	5–12	3518	10.2	EAPD
Greece	[95]	8 & 14	2335	21	EAPD
India	Parikh et al. [141]	8–12	1366	9.2	EAPD
India	Bhaskar and Hegde [15]	8–13	1173	9.5	EAPD
India	Mittal et al. [126]	6–9	1792	6.3	EAPD
India	Kirthiga et al. [97]	11–16	2000	8.9	EAPD
India	Krishnah et al. [101]	9–14	4989	7.3	EAPD
India	Yannam et al. [211]	8–12	2486	9.7	EAPD
India	Mishra and Pandey [124]	8–12	1369	13.9	EAPD
India	Mittal et al. [127]	6–12	886	7.1	EAPD
India	Subramaniam et al. [182]	7–9	2500	0.5	EAPD
India	Samuel et al. [159]	8–12	4495	5.25	EAPD
India	Padavala and Sukumaran [140]	7–12	170	12.9	EAPD
India	Rai et al. [148]	7–9	992	21.4	mDDE
Iran	Ghanim et al. [63]	9–11	810	20.2	EAPD
Iran	Poureslami et al. [146]	7–12	779	6.5	EAPD
Iran	Salem et al. [158]	6–13	553	18.4	EAPD
Iraq	Ghanim et al. [66]	7–9	823	18.6	EAPD
Italy	Calderara et al. [22]	7–8	227	13.7	Calderara
Italy	Condo et al. [30]	4–14	1500	7.3	EAPD
Japan	Saitoh et al. [156]		4496	19.8	EAPD

(continued)

Table 10.5 (continued)

Country	Authors	Age (years)	Sample Size	Defect prevalence (%)	Criteria
Jordan	Zawaideh et al. [213]	8.4	3241	17.6	EAPD
Kenya	Kemoli [94]	6–8	3591	13.7	Kemoli [94]
Korea	Shin et al. [171]	14–16	1371	13.8	EAPD
Libya	Fteita et al. [57]	7–9	378	2.9	Calderara et al. [22]
Lithuania	Jasulaityte et al. [89]	7–9	1277	9.7	EAPD
Malaysia	Nik-Hussain et al. [135]	16	4085	15 (demarcated)	mDDE
Malaysia	Hussain et al. [83]	7–12	154	16.9	EAPD
Mexico	Gurrusquieta et al. [72]	6–12	1156	15.8	EAPD
Nepal	Shrestha et al. [172]	7–12	749	13.7	EAPD
Nepal	Meisheri et al. [123]	7–13	567	8.6	
New Zealand	Mahoney and Morrison [118]	7–10	522	14.9	mDDE
New Zealand	Mahoney and Morrison [119]	7–10	234	18.8/15.7	mDDE/EAPD
Nigeria	Oyedale et al. [138]	8–10	469	17.7	EAPD
Nigeria	Temilola et al. [185]	8–10	236	9.7	Kemoli [94]
Nigeria	Folayan et al. [55]	6–16	853	2.9	EAPD
Norway	Schmalfuss et al. [161]	16	794	13.9	EAPD
Saudi Arabia	Allazzam et al. [6]	8–12	267	8.6	EAPD
Saudi Arabia	Al-Hammad et al. [2]	8–10	924	40.7	EAPD
Saudi Arabia	Rizk et al. [150]	7–9	411	25.1	EAPD
Serbia	Martinovic et al. [121]	8–10	712	12.2	EAPD
Singapore	Ng et al. [134], Ng et al. (2015)	7.7	1083	12.5	EAPD
Slovenia	Groselj and Jan [70]	6–11.5	478	21.4	mDDE; EAPD
Spain	Comes Martinez et al. [29]	-	193	12.4	EAPD
Spain	Martinez Gomez et al. [120]	6–14	505	17.8	EAPD
Spain	Garcia-Margarit et al. [60]	8	840	21.8	EAPD
Spain	Negre-Barber et al. [132]	8–9	414	24.2	EAPD
Spain	Hernandez et al. [79]	6–14	705	7.9	EAPD
Sweden	Koch et al. [98]	9–13	2252	3.6–14.4	Koch
Sweden	Jälevik et al. [86]	7–8	516	18.4	mDDE
Sweden	Brogardh-Roth et al. [18]	10–12	82	16	EAPD
Sweden	Jälevik et al. [87]	11–19	796	12.2	mDDE
Thailand	Savisit et al. [160] Abstract	6–7	627	20.3	EAPD

Table 10.5 (continued)

Country	Authors	Age (years)	Sample Size	Defect prevalence (%)	Criteria
Thailand	Pitiphat et al. [144]	7–8	282	27.7	EAPD
The Netherlands	Weerheijm et al. [200]	11	497	9.7	Weerheijm
The Netherlands	Jasulaityte et al. [90]	9	442	14.3	Weerheijm
The Netherlands	Elfrink et al. [46]	6	6161	8.7	EAPD
Turkey	Kuscu et al. [106]	7–9	147	14.9	EAPD
Turkey	Kuscu et al. [105]	7–10	197	9.1/9.2	EAPD
Turkey	Sonmez et al. [177]	7–12	4049	7.7	EAPD
Turkey	Koruyucu et al. [100]	8–11	1511	14.2	EAPD
United Arab Emirates	Hussian et al. [82]	12	342	27.2	EAPD
Uruguay	López Jordi et al. [113]	7–17	626	12.3	Weerheijm
Uruguay	Biondi et al. [17]	11	463	7.1	Weerheijm

mDDE will have demarcated opacities on first permanent molars and/or incisors
Alaluusua et al. [3]; Cabral [21]; Calderara et al. [22]; Research & Epidemiology FDI Commission on Oral Health [53]; Clarkson and O'Mullane [27]; Weerheijm et al. [199]; Kemoli [94]; Koch et al. [98]; Weerheijm et al. [200]

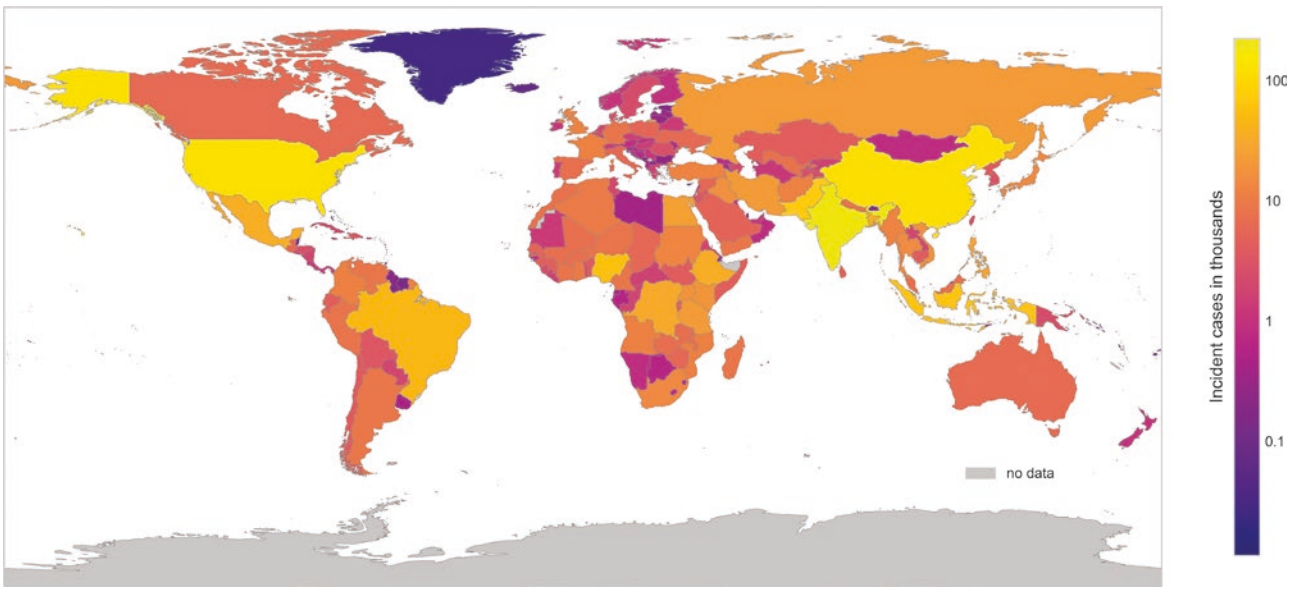


Fig. 10.6 MIH prevalence worldwide

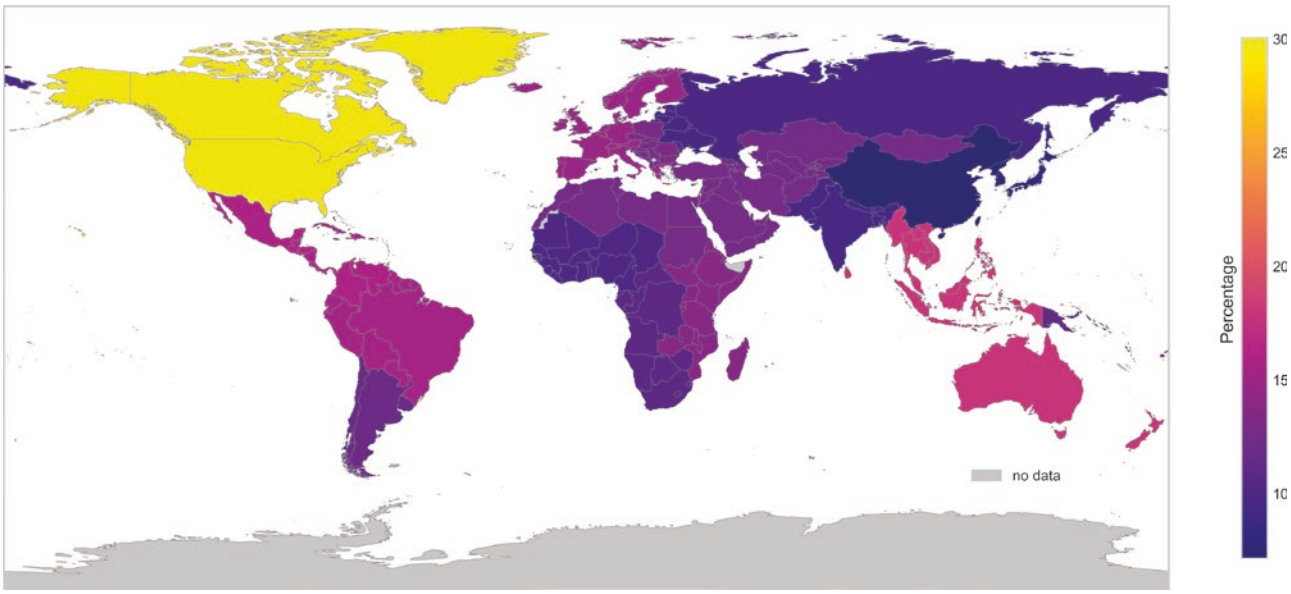


Fig. 10.7 Global Burden of MIH

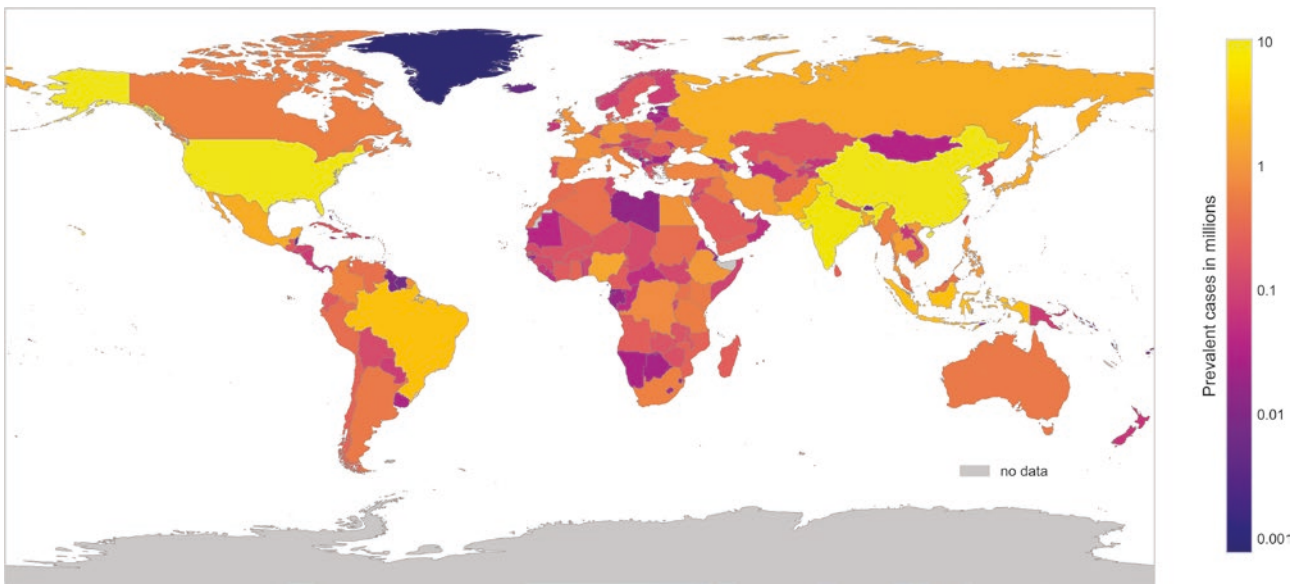


Fig. 10.8 MIH global burden

10.5 Summary

DDE are highly prevalent worldwide. Many arise from maternal illness during pregnancy and/or childhood illness during the developmental period of the teeth; and another less prevalent but no less important heterogeneous group is genetically linked. Two major types of defect exist – quantitative (hypoplasia) and qualitative (hypomineralisation), with wide variation in presentation and location on the teeth.

Early diagnosis of DDE is important to maximise the long-term prognosis of the affected teeth. The clinical consequences of DDE vary considerably – from rapid breakdown of tooth structure soon after eruption, sensitivity and pain to unaesthetic appearance; and they create a large burden on health expenditure.

The importance of DDE should be promulgated widely in the dental community, and especially amongst the general population – as early recognition of DDE and comprehension of their implications is vital. The ultimate goal would be their elimination; however, at this time, this goal is only aspirational.

Point of Emphasis

- DDE are prevalent defects and can have a profound effect on the oral health of the affected individual.
- There is great a variability of presentations, from qualitative to quantitative defects, that is, hypomineralisation and hypoplasia of enamel.
- Aetiology may be local or systemic and individual genetics can also influence or cause DDE, with both single-gene effects and multiple/poly-gene effects evident.
- Early and correct diagnosis is important so that correct treatment can be provided and the impact of the defect minimised.

References

1. Akcam MO, Evirgen S, Uslu O, Memikoglu UT. Dental anomalies in individuals with cleft lip and/or palate. Eur J Orthod. 2010;32(2):207–13.
2. Al-Hammad NS, Al-Dhubaiban M, Alhowaish L, Bello LL. Prevalence and clinical characteristics of molar-incisor-hypomineralization in school children in Riyadh, Saudi Arabia. Int J Med Sci Clin Invent. 2018;5(3):3570–6.
3. Alaluusua S, Lukinmaa P-L, Vartiainen T, Partanen M, Torppa J, Tuomisto J. Polychlorinated dibenzo-p-dioxins and dibenzofurans via mother's milk may cause developmental defects in the child's teeth. Environ Toxicol Pharmacol. 1996;1(3):193–7.
4. Aldred MJ, Savarirayan R, Crawford PJ. Amelogenesis imperfecta: a classification and catalogue for the 21st century. Oral Dis. 2003;9(1):19–23.
5. Allam EP, Ghoneima A, Tholpady SS, Kula K. Enamel hypomineralization in children with clefts and the relationship to treatment: a cross-sectional retrospective study. Ann Plast Surg. 2018;81(5):544–7.
6. Allazzam SM, Alaki SM, El Meligy OAS. Molar incisor hypomineralization, prevalence, and etiology. Int J Dent. 2014;2014:1–8.
7. Altug-Atac AT, Erdem D. Prevalence and distribution of dental anomalies in orthodontic patients. Am J Orthod Dentofacial Orthop. 2007;131(4):510–4.
8. Americano GCA, Jacobsen PE, Soviero VM, Haubek D. A systematic review on the association between molar incisor hypomineralization and dental caries (review). Int J Paediatr Dent. 2017;27(1):11–21.
9. Americano GCA, Jorge RC, Moliterno LFM, Soviero VM. Relating molar incisor hypomineralization and caries experience using the decayed, missing, or filled index (article). Pediatr Dent. 2016;38(5):419–24. <Go to ISI>://WOS:000387097400009.
10. Arrow P. Prevalence of developmental enamel defects of the first permanent molars among school children in Western Australia. Aust Dent J. 2008;53(3):250–9.
11. Bäckman B, Holm A-K. Amelogenesis imperfecta: prevalence and incidence in a northern Swedish county. Community Dent Oral Epidemiol. 1986;14(1):43–7.
12. Balmer R, Toumba J, Godson J, Duggal M. The prevalence of molar incisor hypomineralisation in Northern England and its relationship to socioeconomic status and water fluoridation (Article). Int J Paediatr Dent. 2012;22(4):250–7.
13. Balmer RC, Laskey D, Mahoney E, Toumba KJ. Prevalence of enamel defects and MIH in non-fluoridated and fluoridated communities. Eur J Paediatr Dent. 2005;6(4):209–12.
14. Bartlett JD. Dental enamel development: proteinases and their enamel matrix substrates. ISRN Dent. 2013;2013:24.
15. Bhaskar S, Hegde S. Molar-incisor hypomineralization: prevalence, severity and clinical characteristics in 8- to 13-year-old children of Udaipur, India (Original Article). Journal of Indian Society of Pedodontics and Preventive Dentistry. 2014;32(4):322–9.
16. Biondi AM, Cortese SG, Martínez K, Ortolani AM, Sebelli PMF, Ienco M, et al. Prevalence of molar incisor hypomineralization in the city of Buenos Aires. Acta Odontol Latinoam. 2011;24(1):81–5.
17. Biondi AM, López Jordi MDC, Cortese SG, Álvarez L, Salveraglio I, Ortolani AM. Prevalence of molar-incisor hypomineralization (MIH) in children seeking dental care at the schools of dentistry of the University of Buenos Aires (Argentina) and University of La República (Uruguay). Acta Odontol Latinoam. 2012;25(2):224–30.
18. Brogardh-Roth S, Matsson L, Klingberg G. Molar-incisor hypomineralization and oral hygiene in 10-to-12-yr-old Swedish children born preterm (Article). Eur J Oral Sci. 2011;119(1):33–9.
19. Buchgraber B, Kqiku L, Ebeleseder KA. Molar incisor hypomineralization: proportion and severity in primary public school children in Graz, Austria (article). Clin Oral Investig. 2018;22(2):757–62.
20. Bussaneli DG, Restrepo M, Fragelli CMB, Santos-Pinto L, Jeremias F, Cordeiro RCL, et al. Genes regulating immune response and amelogenesis interact in increasing the susceptibility to molar-incisor hypomineralization. Caries Res. 2019;53(2):217–27.
21. Cabral RN. Novo sistema de detecção para a hipomineralização molar incisivo: diagnóstico, progressão dos defeitos e decisão de tratamento. Brasília: Universidade de Brasília; 2017.
22. Calderara PC, Gerthoux PM, Mocarelli P, Lukinmaa PL, Tramacere PL, Alaluusua S. The prevalence of Molar Incisor Hypomineralisation (MIH) in a group of Italian school children. Eur J Paediatr Dent. 2005;6(2):79–83. http://europepmc.org/abstract/MED/16004536.
23. Casanova-Rosado A, Medina-Solís C, Casanova-Rosado J, Vallejos-Sánchez A, Martinez-Mier E, Loyola-Rodríguez J, et al. Association between developmental enamel defects in the primary and permanent dentitions. Eur J Paediatr Dent. 2011;12(3):155–8.
24. Chaves A, Rosenblatt A, Oliveira A. Enamel defects and its relation to life course events in primary dentition of Brazilian children: a longitudinal study. Community Dent Health. 2007;24:31–6.
25. Cho SY, Ki Y, Chu V. Molar incisor hypomineralization in Hong Kong Chinese children (article). Int J Paediatr Dent. 2008;18(5):348–52.
26. Chosack A, Eidelman E, Wisotski I, Cohen T. Amelogenesis imperfecta among Israeli Jews and the description of a new type of local hypoplastic autosomal recessive amelogenesis imperfecta. Oral Surg Oral Med Oral Pathol. 1979;47(2):148–56.
27. Clarkson J, O'Mullane D. A modified DDE index for use in epidemiological studies of enamel defects. J Dent Res. 1989;68(3):445–50.
28. Clarkson JJ, O'Mullane DM. Prevalence of enamel defects/fluorosis in fluoridated and non-fluoridated areas in Ireland. Community Dent Oral Epidemiol. 1992;20(4):196–9.
29. Comes Martínez Á, De la Puente Ruiz C, Rodríguez Salvanés F. Prevalencia de Hipomineralización en primeros molares permanentes (MIH) en población infantil del Área 2 de Madrid. RCOE. 2007;12:129–34. http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1138-123X2007000200002&nrm=iso.

30. Condò R, Perugia C, Maturo P, Docimo R. MIH: epidemiologic clinic study in paediatric patient. ORAL Implantol. 2012;5(2–3):58–69. https://www.ncbi.nlm.nih.gov/pubmed/23285408, https://www.ncbi.nlm.nih.gov/pmc/PMC3505102/.
31. Cortines AADO, Corrêa-Faria P, Paulsson L, Costa PS, Costa LR. Developmental defects of enamel in the deciduous incisors of infants born preterm: Prospective cohort. Oral Dis. 2019;25:543–9.
32. Costa FS, Silveira ER, Pinto GS, Nascimento GG, Thomson WM, Demarco FF. Developmental defects of enamel and dental caries in the primary dentition: a systematic review and meta-analysis. J Dent. 2017;60:1–7.
33. Crawford PJM, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. Orphanet J Rare Dis. 2007;2:17.
34. Crombie F, Manton D, Kilpatrick N. Aetiology of molar–incisor hypomineralization: a critical review. Int J Paediatr Dent. 2009;19(2):73–83.
35. Crombie FA, Manton DJ, Palamara JEA, Zalizniak I, Cochrane NJ, Reynolds EC. Characterisation of developmentally hypomineralised human enamel (article). J Dent. 2013;41(7):611–8.
36. Da Costa-Silva CM, Ambrosano GMB, Jeremias F, De Souza JF, Mialhe FL. Increase in severity of molar–incisor hypomineralization and its relationship with the colour of enamel opacity: a prospective cohort study. Int J Paediatr Dent. 2011;21(5):333–41.
37. da Costa-Silva CM, Jeremias F, de Souza JF, Cordeiro RDL, Santos-Pinto L, Zuanon ACC. Molar incisor hypomineralization: prevalence, severity and clinical consequences in Brazilian children (Article). Int J Paediatr Dent. 2010;20(6):426–34.
38. da Costa Silva CM, Ortega EMM, Mialhe FL. The impact of molar-incisor hypomineralisation on dental caries in permanent first molars: a prospective cohort study. Oral Health Prev Dent. 2017;15(6):581–6.
39. Dantas-Neta NB, Soares Figueiredo M, Lima CCB, Bendo CB, Matos de Andrade ÉM, Lima MDDM, et al. Factors associated with molar–incisor hypomineralisation in schoolchildren aged 8–10 years: a case–control study. Int J Paediatr Dent. 2018;28(6):570–7.
40. de Lima MDD, Andrade MJB, Dantas-Neta NB, Andrade NS, Teixeira R, de Moura MS, et al. Epidemiologic study of molar-incisor hypomineralization in schoolchildren in Northeastern Brazil (article). Pediatr Dent. 2015;37(7):513–9. <Go to ISI>://WOS:000367771900004.
41. Dietrich G, Sperling S, Hetzer G. Molar incisor hypomineralisation in a group of children and adolescents living in Dresden (Germany). Eur J Paediatr Dent. 2003;4(3):133–7.
42. Elfrink MEC, Ghanim A, Manton DJ, Weerheijm KL. Standardised studies on Molar Incisor Hypomineralisation (MIH) and Hypomineralised Second Primary Molars (HSPM): a need (article). Eur Arch Paediatr Dent. 2015;16(3):247–55.
43. Elfrink MEC, Moll HA, Kiefte-de Jong JC, El Marroun H, Jaddoe VWV, Hofman A, et al. Is maternal use of medicines during pregnancy associated with deciduous molar hypomineralisation in the offspring? A prospective, population-based study (article). Drug Saf. 2013;36(8):627–33.
44. Elfrink MEC, Moll HA, Kiefte-de Jong JC, Jaddoe VWV, Hofman A, ten Cate JM, et al. Pre- and postnatal determinants of deciduous molar hypomineralisation in 6-year-old children. The generation R study (article). Plos One. 2014;9(7):8.
45. Elfrink MEC, Schuller AA, Weerheijm KL, Veerkamp JSJ. Hypomineralized second primary molars: prevalence data in Dutch 5-year-olds. Caries Res. 2008;42(4):282–5.
46. Elfrink MEC, Ten Cate JM, Jaddoe VWV, Hofman A, Moll HA, Veerkamp JSJ. Deciduous molar hypomineralization and molar incisor hypomineralization (article). J Dent Res. 2012;91(6):551–5.
47. Elfrink MEC, Veerkamp JSJ, Aartman IHA, Moll HA, Ten Cate JM. Validity of scoring caries and primary molar hypomineralization (DMH) on intraoral photographs (journal article). Eur Arch Paediatr Dent. 2009;10(1):5–10.
48. Elhennawy K, Manton DJ, Crombie F, Zaslansky P, Radlanski RJ, Jost-Brinkmann P-G, et al. Structural, mechanical and chemical evaluation of molar-incisor hypomineralization-affected enamel: a systematic review. Arch Oral Biol. 2017;83:272–81.
49. Elhennawy K, Schwendicke F. Managing molar-incisor hypomineralization: a systematic review (review). J Dent. 2016;55:16–24.
50. Elliott J. Structure, crystal chemistry and density of enamel apatites. In: Chadwick D, Cardew G, editors, Ciba Foundation Symposium 205 - dental enamel. Ciba Foundation; 1997. p. 54–72.
51. Farah RA, Swain MV, Drummond BK, Cook R, Atieh M. Mineral density of hypomineralised enamel (Article). J Dent. 2010;38(1):50–8.
52. Farsi N. Developmental enamel defects and their association with dental caries in preschoolers in Jeddah, Saudi Arabia. Oral Health Prev Dent. 2010;8(1):85–92.
53. FDI Commission on Oral Health, Research and Epidemiology. An epidemiological index of developmental defects of dental enamel (D.D.E. Index). Int Dent J. 1982;32:159–67.
54. FDI Commission on Oral Health, Research & Epidemiology. Report of an FDI Working Group. A review of the developmental defects of enamel index (DDE Index). Int Dent J. 1992;42(6):411–26.
55. Folayan MO, Oyedele TA, Oziegbe E. Time expended on managing molar incisor hypomineralization in a pediatric dental clinic in Nigeria (article). Braz Oral Res. 2018;32:8.
56. Frencken JE, Peters MC, Manton DJ, Leal SC, Gordan VV, Eden E. Minimal intervention dentistry for managing dental caries - a review. Int Dent J. 2012;62(5):223–43.
57. Fteita D, Ali A, Alaluusua S. Molar-incisor hypomineralization (MIH) in a group of school-aged children in Benghazi, Libya (journal article). Eur Arch Paediatr Dent. 2006;1(2):92–5.
58. Gambetta-Tessini K, Marino R, Ghanim A, Calache H, Manton DJ. Carious lesion severity and demarcated hypomineralized lesions of tooth enamel in schoolchildren from Melbourne, Australia (article). Aust Dent J. 2018;63(3):365–73.
59. Gambetta-Tessini K, Mariño R, Ghanim A, Calache H, Manton DJ. The impact of MIH/HSPM on the carious lesion severity of schoolchildren from Talca, Chile (journal article). Eur Arch Paediatr Dent. 2019.
60. Garcia-Margarit M, Catala-Pizarro M, Montiel-Company JM, Almerich-Silla JM. Epidemiologic study of molar-incisor hypomineralization in 8-year-old Spanish children (article). Int J Paediatr Dent. 2014;24(1):14–22.
61. Garot E, Couture-Veschambre C, Manton D, Beauval C, Rouas P. Analytical evidence of enamel hypomineralisation on permanent and primary molars amongst past populations. Sci Rep. 2017a;7(1):1712.
62. Garot E, Couture-Veschambre C, Manton D, Rodriguez V, Lefrais Y, Rouas P. Diagnostic guide enabling distinction between taphonomic stains and enamel hypomineralisation in an archaeological context. Arch Oral Biol. 2017b;74:28–36.
63. Ghanim A, Bagheri R, Golkari A, Manton D. Molar–incisor hypomineralisation: a prevalence study amongst primary schoolchildren of Shiraz, Iran (journal article). Eur Arch Paediatr Dent. 2014;15(2):75–82.

64. Ghanim A, Manton D, Marino R, Morgan M, Bailey D. Prevalence of demarcated hypomineralisation defects in second primary molars in Iraqi children (article). Int J Paediatr Dent. 2013;23(1):48–55.
65. Ghanim A, Mariño R, Manton DJ. Validity and reproducibility testing of the Molar Incisor Hypomineralisation (MIH) Index. Int J Paediatr Dent. 2019;29(1):6–13.
66. Ghanim A, Morgan M, Marino R, Bailey D, Manton D. Molar-incisor hypomineralisation: prevalence and defect characteristics in Iraqi children (article). Int J Paediatr Dent. 2011;21(6):413–21.
67. Ghanim A, Silva MJ, Elfrink MEC, Lygidakis NA, Marino RJ, Weerheijm KL, et al. Molar incisor hypomineralisation (MIH) training manual for clinical field surveys and practice (article). Eur Arch Paediatr Dent. 2017;18(4):225–42.
68. Goodman A. Dental enamel hypoplasias in prehistoric populations. Adv Dent Res. 1989;3(2):265–71.
69. Gravina D, Cruvinel V, Azevedo T, Toledo O, Bezerra A. Enamel defects in the primary dentition of preterm and full term children. J Clin Pediatr Dent. 2013;37(4):391–5.
70. Groselj M, Jan J. Molar incisor hypomineralisation and dental caries among children in Slovenia (Article). Eur J Paediatr Dent. 2013;14(3):241–5. <Go to ISI>://WOS:000325310600015.
71. Gupta SK, Saxena P, Jain S, Jain D. Prevalence and distribution of selected developmental dental anomalies in an Indian population. J Oral Sci. 2011;53(2):231–8.
72. Gurrusquieta BJ, Nunez VMM, Lopez M. Prevalence of molar incisor hypomineralization in Mexican children (article). Journal of Clinical Pediatric Dentistry. 2017;41(1):18–21. <Go to ISI>://WOS:000405376900004.
73. Hall RK. The prevalence of developmental defects of tooth enamel (DDE) in a pediatric hospital department of dentistry population (part I). Adv Dent Res. 1989;3(2):114–9.
74. Hall RK. Pediatric orofacial medicine and pathology. Melbourne: Chapman & Hall Medical; 1994.
75. Hall RK, Phakey P, Palamara J, McCredie DA. Amelogenesis imperfecta and nephrocalcinosis syndrome: case studies of clinical features and ultrastructure of tooth enamel in two siblings. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;79(5):583–92.
76. Hargreaves JA, Cleaton-Jones PE, Williams SDL. Hypocalcification and hypoplasia in permanent teeth of children from different ethnic groups in South Africa assessed with a new index. Adv Dent Res. 1989;3(2):126–31.
77. Harrison M, Cameron A, Kilpatrick N. Syndromes and diseases associated with developmental defects of enamel. In: Drummond BK, Kilpatrick N, editors. Planning and care for children and adolescents with dental enamel defects: etiology, research and contemporary management. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015. p. 45–58.
78. Heitmuller D, Thiering E, Hoffmann U, Heinrich J, Manton D, Kuhnisch J, et al. Is there a positive relationship between molar incisor hypomineralisations and the presence of dental caries? (article). Int J Paediatr Dent. 2013;23(2):116–24.
79. Hernandez M, Boj JR, Espasa E, Peretz B. First permanent molars and permanent incisors teeth by tooth prevalence of molar-incisor-hypomineralisation in a group of Spanish schoolchildren (article). Acta Stomatol Croat. 2018;52(1):4–11.
80. Hoffman MP, Cutress TW, Tomiki S. Prevalence of developmental defects of enamel in children in the Kingdom of Tonga. New Zealand Dental Journal. 1988;84(375):7–10. http://europepmc.org/abstract/MED/3164452.
81. Hoffmann RHS, Sousa MDLRD, Cypriano S. Prevalência de defeitos de esmalte e sua relação com cárie dentária nas dentições decídua e permanente, Indaiatuba, São Paulo, Brasil. Cad Saude Publica. 2007;23:435–44. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-311X2007000200020&nrm=iso.
82. Hussain G, Al-Halabi M, Kowash M, Hassan A. The prevalence and severity of molar incisor hypomineralization and molar hypomineralization in Dubai, UAE. J Dent Child. 2018;85(3):102–7. https://www.ingentaconnect.com/content/aapd/jodc/2018/00000085/00000003/art00002.
83. Hussein AS, Faisal M, Haron M, Ghanim AM, Abu-Hassan MI. Distribution of molar incisor hypomineralization in Malaysian children attending university dental clinic (article). Journal of Clinical Pediatric Dentistry. 2015;39(3):219–23.
84. Hysi D, Kuscu OO, Droboniku E, Toti C, Xhemnica L, Caglar E. Prevalence and aetiology of Molar-Incisor Hypomineralisation among children aged 8–10 years in Tirana, Albania (article). Eur J Paediatr Dent. 2016;17(1):75–9. <Go to ISI>://WOS:000377704800015.
85. Jacobsen PE, Henriksen TB, Haubek D, Østergaard JR. Developmental enamel defects in children prenatally exposed to anti-epileptic drugs. PLoS One. 2013;8(3):e58213.
86. Jälevik B, Klingberg G, Barregård L, Norén JG. The prevalence of demarcated opacities in permanent first molars in a group of Swedish children AU - Jälevik, Birgitta. Acta Odontol Scand. 2001;59(5):255–60.
87. Jälevik B, Szigyarto-Matei A, Robertson A. The prevalence of developmental defects of enamel, a prospective cohort study of adolescents in Western Sweden: a Barn I TAnadvarden (BITA, children in dental care) study (journal article). Eur Arch Paediatr Dent. 2018;19(3):187–95.
88. Jankovic S, Ivanovic M, Davidovic B, Lecic J. Distribution and characteristics of molar-incisor hypomineralization (Article). Vojnosanit Pregl. 2014;71(8):730–4.
89. Jasulaityte L, Veerkamp JS, Weerheijm KL. Molar incisor hypomineralization: review and prevalence data from a study of primary school children in Kaunas (Lithuania) (journal article). Eur Arch Paediatr Dent. 2007;8(2):87–94.
90. Jasulaityte L, Weerheijm KL, Veerkamp JS. Prevalence of Molar-Incisor-Hypomineralisation among children participating in the Dutch National Epidemiological Survey (2003) (journal article). Eur Arch Paediatr Dent. 2008;9(4):218–23.
91. Jeremias F, de Souza JF, Silva CMD, Cordeiro RDL, Zuanon ACC, Santos-Pinto L. Dental caries experience and Molar-Incisor Hypomineralization (article). Acta Odontol Scand. 2013;71(3–4):870–6.
92. Kanchanakamol U, Tuongratanaphan S, Tuongratanaphan S, Lertpoonvilaikul W, Chittaisong C, Pattanaporn K, et al. Prevalence of developmental enamel defects and dental caries in rural pre-school Thai children. Community Dent Health. 1996;13:204–7.
93. Kar S, Sarkar S, Mukherjee A. Prevalence and distribution of developmental defects of enamel in the primary dentition of IVF children of West Bengal. J Clin Diagn Res. 2014;8(7):ZC73–6.
94. Kemoli AM. Prevalence of molar incisor hypomineralisation in six to eight year-olds in two rural divisions in Kenya. East Afr Med J. 2008;85(10):514–9.
95. Kevrekidou A, Kosma I, Arapostathis K, Kotsanos N. Molar incisor hypomineralization of eight- and 14-year-old children: prevalence, severity, and defect characteristics (article). Pediatr Dent. 2015;37(5):455–61. <Go to ISI>://WOS:000364360700009.
96. King NM. Developmental defects of enamel in Chinese girls and boys in Hong Kong. Adv Dent Res. 1989;3(2):120–5.
97. Kirthiga M, Poornima P, Praveen R, Gayathri P, Manju M, Priya M. Prevalence and severity of molar incisor hypomineralization in children aged 11–16 years of a city in Karnataka, Davangere (original article). J Indian Soc Pedod Prev Dent. 2015;33(3):213–7.

98. Koch G, Hallonsten A-L, Ludvigsson N, Hansson BO, Hoist A, Ullbro C. Epidemiologic study of idiopathic enamel hypomineralization in permanent teeth of Swedish children. Community Dent Oral Epidemiol. 1987;15(5):279–85.
99. Kohlboeck G, Heitmueller D, Neumann C, Tiesler C, Heinrich J, Heinrich-Weltzien R, et al. Is there a relationship between hyperactivity/inattention symptoms and poor oral health? Results from the GINIplus and LISAplus study. Clin Oral Investig. 2013;17(5):1329–38.
100. Koruyucu M, Özel S, Tuna EB. Prevalence and etiology of molar-incisor hypomineralization (MIH) in the city of Istanbul. J Dent Sci. 2018;13(4):318–28.
101. Krishnan R, Ramesh M, Chalakkal P. Prevalence and characteristics of MIH in school children residing in an endemic fluorosis area of India: an epidemiological study (article). Eur Arch Paediatr Dent. 2015;16(6):455–60.
102. Kűhnisch J, Heitmuller D, Thiering E, Brockow I, Hoffmann U, Neumann C, et al. Proportion and extent of manifestation of molar-incisor-hypomineralizations according to different phenotypes (article). J Public Health Dent. 2014;74(1):42–9.
103. Kühnisch J, Lauenstein A, Pitchika V, McGlynn G, Staskiewicz A, Hickel R, et al. Was molar incisor hypomineralisation (MIH) present in archaeological case series? (journal article). Clin Oral Investig. 2016;20(9):2387–93.
104. Kukleva MP, Petrova S, Kondeva V, Nihtyanova T. Molar incisor hypomineralisation in 7-to-14-year old children in Plovdiv, Bulgaria--an epidemiologic study. Folia Med (Plovdiv). 2008;50(3):71–5.
105. Kuscu OO, Caglar E, Aslan S, Durmusoglu E, Karademir A, Sandalli N. The prevalence of molar incisor hypomineralization (MIH) in a group of children in a highly polluted urban region and a windfarm-green energy island (article). Int J Paediatr Dent. 2009;19(3):176–85.
106. Kuscu OO, Caglar E, Sandalli N. The prevalence and aetiology of molar-incisor hypomineralisation in a group of children in Istanbul (article). Eur J Paediatr Dent. 2008;9(3):139–44. <Go to ISI>://WOS:000268594400006.
107. Lacruz R, Habelitz S, Wright J, Paine M. Dental enamel formation and implications for oral health and disease. Physiol Rev. 2017;97(3):939–93.
108. Lai PY, Seow WK, Tudehope DI, Rogers Y. Enamel hypoplasia and dental caries in very-low birthweight children: a case-controlled, longitudinal study. Pediatr Dent. 1997;19(1):42–9.
109. Lenzi MM, Alexandria AK, Ferreira DMTP, Maia LC. Does trauma in the primary dentition cause sequelae in permanent successors? A systematic review. Dent Traumatol. 2015;31(2):79–88.
110. Leppäniemi A, Lukinmaa P-L, Alaluusua S. Nonfluoride hypomineralizations in the permanent first molars and their impact on the treatment need. Caries Res. 2001;35(1):36–40.
111. Li Y, Chen X, Chen S, Janal MN, Sarnat H. Developmental defects of enamel increase caries susceptibility in Chinese preschool children. Community Dent Oral Epidemiol. 2018;46(5):500–10.
112. Li Y, Navia JM, Bian J-Y. Prevalence and distribution of developmental enamel defects in primary dentition of Chinese children 3–5 years old. Community Dent Oral Epidemiol. 1995;23(2):72–9.
113. López Jordi MC, Cortese SG, Alvarez L, Salveraglio I, Ortolani AM, Biondi AM. Comparison of the prevalence of molar incisor hypomineralization among children with different health care coverage in the cities of Buenos Aires (Argentina) and Montevideo (Uruguay). Salud Colect. 2014;10(2):243–51.
114. Lunardelli SE, Peres MA. Prevalence and distribution of developmental enamel defects in the primary dentition of pre-school children. Braz Oral Res. 2005;19:144–9. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-83242005000200013&nrm=iso.
115. Lygidakis NA, Dimou G, Briseniou E. Molar-incisor-hypomineralisation (MIH). Retrospective clinical study in Greek children. I. Prevalence and defect characteristics (journal article). Eur Arch Paediatr Dent. 2008;9(4):200–6.
116. Macho VMP, Coelho AS, Veloso E, Silva DM, Andrade DJCD. Oral manifestations in pediatric patients with coeliac disease – a review article. Open Dent J. 2017;11(1).
117. Mackay TD, Thomson WM. Enamel defects and dental caries among Southland children. New Zealand Dental Journal. 2005;101(2):35–43.
118. Mahoney EK, Morrison DG. The prevalence of molar-incisor hypomineralisation (MIH) in Wainuiomata children. N Z Dent J. 2009;105(4):121–7.
119. Mahoney EK, Morrison DG. Further examination of the prevalence of MIH in the Wellington region. New Zealand Dental Journal. 2011;107(3):79–84. http://europepmc.org/abstract/MED/21957834.
120. Martinez Gomez TP, Guinot Jimeno F, Bellet Dalmau LJ, Ginet Tarrida L. Prevalence of molar–incisor hypomineralisation observed using transillumination in a group of children from Barcelona (Spain). Int J Paediatr Dent. 2012;22(2):100–9.
121. Martinovic B, Ivanovic M, Cvetkovic A, Todic J, Milojkovic Z, Pavlovic J, et al. Prevalence, characteristics and severity of hypomineralization of the first permanent molars and incisors in children from the northern part of Kosovo and Metohija (article). Srp Arh Celok Lek. 2017;145(7-8):364–9.
122. McKay S, Farah R, Broadbent JM, Tayles N, Halcrow SE. Is it health or the burial environment: differentiating between hypomineralised and post-mortem stained enamel in an archaeological context. PLoS One. 2013;8(5):e64573.
123. Meisheri DJ, Devasya A, Giri DK, Acharya R, Jha M. Prevalence of molar-incisor hypomineralization in 7–13 years old children of Biratnagar, Nepal: a cross sectional study. Int J Curr Res Rev. 2018;10(11):7–10.
124. Mishra A, Pandey RK. Molar incisor hypomineralization: an epidemiological study with prevalence and etiological factors in Indian pediatric population. Int J Clin Pediatr Dent. 2016;9(2):167–71.
125. Mittal N, Sharma BB. Hypomineralised second primary molars: prevalence, defect characteristics and possible association with molar incisor hypomineralisation in Indian children (article). Eur Arch Paediatr Dent. 2015;16(6):441–7.
126. Mittal NP, Goyal A, Gauba K, Kapur A. Molar incisor hypomineralisation: prevalence and clinical presentation in school children of the northern region of India (journal article). Eur Arch Paediatr Dent. 2014;15(1):11–8.
127. Mittal R, Chandak S, Chandwani M, Singh P, Pimpale J. Assessment of association between molar incisor hypomineralization and hypomineralized second primary molar (article). J Int Soc Prev Community Dent. 2016;6(1):34–9.
128. Montero M, Douglass J, Mathieu G. Prevalence of dental caries and enamel defects in Connecticut head start children. Pediatr Dent. 2003;25:235–9.
129. Mulic A, Cehajic E, Tveit AB, Stenhagen KR. How serious is molar incisor hypomineralisation (MIH) among 8-and 9-year-old children in Bosnia-Herzegovina? A clinical study (article). Eur J Paediatr Dent. 2017;18(2):153–7. <Go to ISI>://WOS:000424078900012.
130. Muratbegovic A, Markovic N, Selimovic MG. Molar incisor hypomineralisation in Bosnia and Herzegovina: prevalence,

aetiology and clinical consequences in medium caries activity population (journal article). Eur Arch Paediatr Dent. 2007;8(4):189–94.
131. Nation W, Matsson L, Peterson J. Developmental enamel defects of the primary dentition in a group of Californian children. J Dent Child. 1987;54:330–4.
132. Negre-Barber A, Montiel-Company JM, Catala-Pizarro M, Almerich-Silla JM. Degree of severity of molar incisor hypomineralization and its relation to dental caries (article). Sci Rep. 2018;8:7.
133. Nelson S, Albert JM, Geng C, Curtan S, Lang K, Miadich S, et al. Increased enamel hypoplasia and very low birthweight infants. J Dent Res. 2013;92(9):788–94.
134. Ng JJ, Eu OC, Nair R, Hong CHL. Prevalence of molar incisor hypomineralization (MIH) in Singaporean children (article). Int J Paediatr Dent. 2015;25(2):73–8.
135. Nik-Hussein NN, Majid ZA, Mutalib KA, Abdullah F, Abang A, Wan MN. Prevalence of developmental defects of enamel among 16-year-old children in Malaysia. Ann Dent Univ Malaya. 1999;6(1):11–6. http://adum.um.edu.my/index.php/adum/article/view/13796.
136. Oliver K, Messer LB, Manton DJ, Kan K, Ng F, Olsen C, et al. Distribution and severity of molar hypomineralisation: trial of a new severity index. Int J Paediatr Dent. 2014;24(2):131–51.
137. Owen ML, Ghanim A, Elsby D, Manton DJ. Hypomineralized second primary molars: prevalence, defect characteristics and relationship with dental caries in Melbourne preschool children (article). Aust Dent J. 2018;63(1):72–80.
138. Oyedele TA, Folayan MO, Adekoya-Sofowora CA, Oziegbe EO, Esan TA. Prevalence, pattern and severity of molar incisor hypomineralisation in 8- to 10-year-old school children in Ile-Ife, Nigeria (article). Eur Arch Paediatr Dent. 2015;16(3):277–82.
139. Oyedele TA, Folayan MO, Oziegbe EO. Hypomineralised second primary molars: prevalence, pattern and associated co morbidities in 8-to 10-year-old children in Ile-Ife, Nigeria (article). BMC Oral Health. 2016;16:7.
140. Padavala S, Sukumaran G. Molar incisor hypomineralization and its prevalence. Contemporary Clinical Dentistry. 2018;9(Suppl 2):S246–50.
141. Parikh DR, Ganesh M, Bhaskar V. Prevalence and characteristics of molar Incisor hypomineralisation (MIH) in the child population residing in Gandhinagar, Gujarat, India (journal article). Eur Arch Paediatr Dent. 2012;13(1):21–6.
142. Petrou MA, Giraki M, Bissar A-R, Wempe C, Schäfer M, Schiffner U, et al. Severity of MIH findings at tooth surface level among German school children (journal article). Eur Arch Paediatr Dent. 2015;16(3):271–6.
143. Petrou MA, Giraki M, Bissar AR, Basner R, Wempe C, Altarabulsi MB, et al. Prevalence of molar-incisor-hypomineralisation among school children in four German cities (article). Int J Paediatr Dent. 2014;24(6):434–40.
144. Pitiphat W, Savisit R, Chansamak N, Subarnbhesaj A. Molar incisor hypomineralization and dental caries in six- to seven-year-old Thai children (article). Pediatr Dent. 2014;36(7):478–82. <Go to ISI>://WOS:000209738900008.
145. Portella PD, Menoncin BLV, De Souza JF, De Menezes JVNB, Fraiz FC, Assunção LRDS. Impact of molar-incisor hypomineralization on quality of life in children with early mixed dentition: a hierarchical approach. Int J Paediatr Dent. 2019.
146. Poureslami H, Shojaiepour R, Abbaspour S, Aminizadeh M, Khademi M, Abbaspour S. Prevalence of the molar incisor hypomineralization in seven to twelve-year-old students of Kerman, Iran, in 2015-2016 (article). J Oral Health Oral Epidemiol. 2018;7(1):21–7.
147. Preusser SE, Ferring V, Wleklinski C, Wetzel WE. Prevalence and severity of molar incisor hypomineralization in a region of Germany - a brief communication (article; proceedings paper). J Public Health Dent. 2007;67(3):148–50.
148. Rai A, Singh A, Menon I, Singh J, Rai V, Aswal GS. Molar incisor hypomineralization: prevalence and risk factors among 7–9 years old school children in Muradnagar, Ghaziabad. Open Dent J. 2018;12:714–22.
149. Raposo F, de Carvalho Rodrigues AC, Lia ÉN, Leal SC. Prevalence of hypersensitivity in teeth affected by molar-incisor hypomineralization (MIH). Caries Res. 2019.
150. Rizk H, Al-Mutairi M, Habibullah M. The prevalence of molar-incisor hypomineralization in primary schoolchildren aged 7–9 years in Qassim Region of Saudi Arabia (report). J Interdiscip Dent. 2018;8:44. https://link.galegroup.com/apps/doc/A541256159/AONE?u=googlescholar&sid=AONE&xid=aae248cc.
151. Robles M-J, Ruiz M, Bravo-Perez M, González E, Peñalver M-A. Prevalence of enamel defects in primary and permanent teeth in a group of schoolchildren from Granada (Spain). Med Oral Patol Oral Cir Bucal. 2012;18(2):e187–93.
152. Rodrigues F, Ribeiro P, Thomaz É, Lima G, Neves P, Ribeiro C. Molar-incisor hypomineralization in schoolchildren of São Luis, Brazil Maranhão: prevalence and associated factors. Braz Res Pediatr Dent Integr Clin. 2015;15(1):271–5.
153. Rugg-Gunn AJ, Al-Mohammadi SM, Butler TJ. Malnutrition and developmental defects of enamel in 2- to 6 -year-old Saudi boys. Caries Res. 1998;32(3):181–92.
154. Ruiz L, Maya R, D'alpino P, Atta M, Da Rocha Svizero N. Prevalence of enamel defects in permanent teeth of patients with complete cleft lip and palate. Cleft Palate Craniofac J. 2013;50(4):394–9.
155. Saber F, Waly N, Moheb D. Prevalence of molar incisor hypomineralisation in a group of Egyptian children using the short form: a cross-sectional study (journal article). Eur Arch Paediatr Dent. 2018;19(5):337–45.
156. Saitoh M, Nakamura Y, Hanasaki M, Saitoh I, Murai Y, Kurashige Y, et al. Prevalence of molar incisor hypomineralization and regional differences throughout Japan (journal article). Environ Health Prev Med. 2018;23(1):55.
157. Salanitri S, Seow W. Developmental enamel defects in the primary dentition: aetiology and clinical management. Aust Dent J. 2013;58(2):133–40.
158. Salem K, Aziz D, Asadi M. Prevalence and predictors of molar incisor hypomineralization (MIH) among rural children in northern Iran (letter). Iran J Public Health. 2016;45(11):1528–30. <Go to ISI>://WOS:000389036700023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5182269/pdf/IJPH-45-1528.pdf.
159. Samuel A, Asokan S, Geethapriya P. Caries status and salivary characteristics of South Indian school children with molar incisor hypomineralization: a cross-sectional study (original article). J Indian Assoc Public Health Dent. 2017;15(2):135–9.
160. Savisit R, Poomat N, Subarnbhesaj A, Pitiphat W. Prevalence of molar incisor hypomineralization in Thai children. J Dent Res. 2008;87(Spec. Iss. B):Abstract 2997.
161. Schmalfuss A, Stenhagen KR, Tveit AB, Crossner CG, Espelid I. Canines are affected in 16-year-olds with molar-incisor hypomineralisation (MIH): an epidemiological study based on the Tromso study: "Fit Futures" (article). Eur Arch Paediatr Dent. 2016;17(2):107–13.
162. Schüler IM, Haberstroh S, Dawczynski K, Lehmann T, Heinrich-Weltzien R. Dental caries and developmental defects of enamel in the primary dentition of preterm infants: case-control observational study. Caries Res. 2018;52(1-2):22–31.

163. Schwendicke F, Elhennawy K, Reda S, Bekes K, Manton DJ, Krois J. Global burden of molar incisor hypomineralization (review). J Dent. 2018;68:10–8.
164. Se MJDF, Ribeiro APD, dos Santos-Pinto LAM, Cordeiro RDL, Cabral RN, Leal SC. Are hypomineralized primary molars and canines associated with molar-incisor hypomineralization? (article). Pediatr Dent. 2017;39(7):445–9. <Go to ISI>://WOS:000425182800006.
165. Seow WK, Wright JT. Diagnosis and management of defects of enamel development. In: Wright JT, editor. Craniofacial and dental developmental defects. Cham: Springer; 2015. p. 81–96.
166. Seow WK, Amaratunge A, Bennett R, Bronsch D, Lai PY. Dental health of aboriginal pre-school children in Brisbane, Australia. Community Dent Oral Epidemiol. 1996;24(3):187–90.
167. Seow WK, Brown JP, Tudehope DI, O'Callaghan M. Developmental defects in the primary dentition of low birth-weight infants: adverse effects of laryngoscopy and prolonged endotracheal intubation. Pediatr Dent. 1984;6(1): 28–31.
168. Seow WK, Ford D, Kazoullis S, Newman B, Holcombe T. Comparison of enamel defects in the primary and permanent dentitions of children from a low-fluoride district in Australia. Pediatr Dent. 2011;33(3):207–12. https://www.ingentaconnect.com/content/aapd/pd/2011/00000033/00000003/art00005.
169. Seow WK, Humphrys C, Tudehope DI. Increased prevalence of developmental dental defects in low birth-weight, prematurely born children: a controlled study. Pediatr Dent. 1987;9(3):221–5.
170. Seow WK, Leishman SJ, Palmer JE, Walsh LJ, Pukallus M, Barnett AG. A longitudinal observational study of developmental defects of enamel from birth to 6 years of age. JDR Clin Transl Res. 2016;1(3):285–91.
171. Shin J, Lee G, Kim J, Kim J, Kim S. Prevalence and clinical features of molar-incisor hypomineralization in adolescents in Yangsan. J Kor Acad Pediatr Dent. 2017;44(2):210–9.
172. Shrestha R, Upadhaya S, Bajracharya M. Prevalence of molar incisor hypomineralisation among school children in Kavre. Kathmandu Univ Med J. 2014;12:38–42.
173. Silva Junior I, Aguiar N, Barros W, da Silva L, Arantes D, Nascimento L. Prevalence and severity of molar incisor hypomineralisation in students of Belem, Brazil. Braz Res Pediatr Dent Intergr Clin. 2015;15(1):377–85.
174. Silva MJ, Scurrah KJ, Craig JM, Manton DJ, Kilpatrick N. Etiology of molar incisor hypomineralization - a systematic review (review). Community Dent Oral Epidemiol. 2016;44(4):342–53.
175. Slayton R, Warren J, Kanellis M, Levy S, Islam M. Prevalence of enamel hypoplasia and isolated opacities in the primary dentition. Pediatr Dent. 2001;23(1):32–6.
176. Smith CEL, Poulter JA, Antanaviciute A, Kirkham J, Brookes SJ, Inglehearn CF, et al. Amelogenesis imperfecta; genes, proteins, and pathways. Front Physiol. 2017;8:435.
177. Sönmez H, Yıldırım G, Bezgin T. Putative factors associated with molar incisor hypomineralisation: an epidemiological study (journal article). Eur Arch Paediatr Dent. 2013;14(6):375–80.
178. Souto-Souza D, da Consolação Soares ME, Rezende VS, de Lacerda Dantas PC, Galvão EL, Falci SGM. Association between developmental defects of enamel and celiac disease: a meta-analysis. Arch Oral Biol. 2018;87:180–90.
179. Souza JF, Costa-Silva CM, Jeremias F, Santos-Pinto L, Zuanon ACC, Cordeiro RCL. Molar incisor hypomineralisation: possible aetiological factors in children from urban and rural areas (journal article). Eur Arch Paediatr Dent. 2012;13(4):164–70.
180. Souza JF, Jeremias F, Costa-Silva CM, Santos-Pinto L, Zuanon ACC, Cordeiro RCL. Aetiology of molar–incisor hypomineralisation (MIH) in Brazilian children (journal article). Eur Arch Paediatr Dent. 2013;14(4):233–8.
181. Soviero V, Haubek D, Trindade C, Da Matta T, Poulsen S. Prevalence and distribution of demarcated opacities and their sequelae in permanent 1st molars and incisors in 7 to 13-year-old Brazilian children (article). Acta Odontol Scand. 2009;67(3):170–5.
182. Subramaniam P, Gupta T, Sharma A. Prevalence of molar incisor hypomineralization in 7–9-year-old children of Bengaluru City, India. Contemp Clin Dent. 2016;7(1):11–5.
183. Sundell S, Koch G. Hereditary amelogenesis imperfecta. I. Epidemiology and clinical classification in a Swedish child population. Swed Dent J. 1985;9(4):157–69.
184. Teixeira R, Andrade NS, Queiroz LCC, Mendes FM, Moura MS, Moura L, et al. Exploring the association between genetic and environmental factors and molar incisor hypomineralization: evidence from a twin study (article). Int J Paediatr Dent. 2018;28(2):198–206.
185. Temilola OD, Folayan MO, Oyedele T. The prevalence and pattern of deciduous molar hypomineralization and molar-incisor hypomineralization in children from a suburban population in Nigeria (article). BMC Oral Health. 2015;15:6.
186. Temple DH. Chronology and periodicity of linear enamel hypoplasia among Late/Final Jomon period foragers: evidence from incremental microstructures of enamel. Quat Int. 2016;405:3–10.
187. Tourino LFPG, Corrêa-Faria P, Ferreira RC, Bendo CB, Zarzar PM, Vale MP. Association between molar incisor hypomineralization in schoolchildren and both prenatal and postnatal factors: a population-based study. Plos One. 2016;11(6):e0156332.
188. Vargas-Ferreira F, Ardenghi TM. Developmental enamel defects and their impact on child oral health-related quality of life. Braz Oral Res. 2011;25:531–7. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-83242011000600010&nrm=iso.
189. Vargas-Ferreira F, Peres MA, Samuel CD, William MT, Demarco FF. Association of pre- peri- and postnatal factors with developmental defects of enamel in schoolchildren. J Clin Pediatr Dent. 2018;42(2):125–34.
190. Vargas-Ferreira F, Salas MMS, Nascimento GG, Tarquinio SBC, Faggion CM, Peres MA, et al. Association between developmental defects of enamel and dental caries: a systematic review and meta-analysis. J Dent. 2015;43(6):619–28.
191. Vasconcelos KR, Arid J, Evangelista S, Oliveira S, Dutra AL, Silva LAB, et al. MMP13 contributes to dental caries associated with developmental defects of enamel. Caries Res. 2019.
192. Vieira AR. On the genetics contribution to molar incisor hypomineralization. Int J Paediatr Dent. 2019a;29(1):2–3.
193. Vieira AR. Prevalence of molar incisor hypomineralisation has a North–South gradient between Europe and North Africa (journal article). Eur Arch Paediatr Dent. 2019b.
194. Vieira AR, Kup E. On the etiology of molar-incisor hypomineralization (article). Caries Res. 2016;50(2):166–9.
195. Vieira AR, Manton DJ. On the variable clinical presentation of molar-incisor hypomineralization. Caries Research, accepted for publication; 2019.
196. Wagner Y. Developmental defects of enamel in primary teeth - findings of a regional German birth cohort study (article). BMC Oral Health. 2017;17:10.

197. Wang Y. Prevalence and presentation patterns of enamel hypomineralisation among paediatric hospital dental patients in Toronto. Canada: University of Toronto; 2018.
198. Weeks KJ, Milsom KM, Lennon MA. Enamel defects in 4- to 5-year-old children in fluoridated and non-fluoridated parts of Cheshire, UK. Caries Res. 1993;27(4):317–20.
199. Weerheijm KL, Duggal M, Mejare I, Papagiannoulis G, Koch G, Martens LC, et al. Judgement criteria for molar incisor hypomineralisation (MIH) in epidemiologic studies: a summary of the European meeting on MIH held in Athens, 2003. Eur J Paediatr Dent. 2003;4(3):110–3.
200. Weerheijm KL, Groen HJ, Beentjes VEVM, Poorterman JHG. Prevalence of cheese molars in eleven-year-old Dutch children. J Dent Child. 2001a;68(4):259–62. https://www.ingentaconnect.com/content/aapd/jodc/2001/00000068/00000004/art00013.
201. Weerheijm KL, Jalevik B, Alaluusua S. Molar-incisor hypomineralisation (article). Caries Res. 2001b;35(5):390–1.
202. Willing N, Pfitzner A, Noren JG, Hoyer I, Glockmann E. Prevalence and causes of developmental defects of enamel. J Dent Res. 2005;84(Spec. Iss):Abstract 473.
203. Witkop C Jr. Hereditary defects in enamel and dentin. Acta Genet. 1957;7:236–9.
204. Witkop CJ Jr. Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification. J Oral Pathol Med. 1989;17(9–10):547–53.
205. Wogelius P, Haubek D, Poulsen S. Prevalence and distribution of demarcated opacities in permanent 1st molars and incisors in 6 to 8-year-old Danish children AU - Wogelius, Pia. Acta Odontol Scand. 2008;66(1):58–64.
206. Wright JT, Carrion IA, Morris C. The molecular basis of hereditary enamel defects in humans. J Dent Res. 2015;94(1):52–61.
207. Wright JT, Meyer BD. Anomalies of the developing dentition. In: Nowak A, Christensen J, Mabry T, Townsend J, Wells M, editors. Pediatric dentistry - infancy through adolescence. Philadelphia: Elsevier; 2019. p. 50–65.
208. Wuollet E, Laisi S, Alaluusua S, Waltimo-Sirén J. The association between molar-incisor hypomineralization and dental caries with socioeconomic status as an explanatory variable in a group of Finnish children. Int J Environ Res Public Health. 2018;15(7):1324.
209. Wuollet E, Laisi S, Salmela E, Ess A, Alaluusua S. Background factors of molar-incisor hypomineralization in a group of Finnish children (article). Acta Odontol Scand. 2014;72(8):963–9.
210. Wuollet E, Laisi S, Salmela E, Ess A, Alaluusua S. Molar–incisor hypomineralization and the association with childhood illnesses and antibiotics in a group of Finnish children AU - Wuollet, Emma. Acta Odontol Scand. 2016;74(5):416–22.
211. Yannam S, Amarlal D, Rekha C. Prevalence of molar incisor hypomineralization in school children aged 8–12 years in Chennai (original article). Journal of Indian Society of Pedodontics and Preventive Dentistry. 2016;34(2):134–8.
212. Yassin SM. Prevalence and distribution of selected dental anomalies among Saudi children in Abha, Saudi Arabia. J Clin Exp Dent. 2016;8(5):e485–90.
213. Zawaideh FI, Al-Jundi SH, Al-Jaljoli MH. Molar incisor hypomineralisation: prevalence in Jordanian children and clinical characteristics (journal article). Eur Arch Paediatr Dent. 2011;12(1):31–6.
214. Zhao DD, Dong B, Yu DD, Ren QQ, Sun YH. The prevalence of molar incisor hypomineralization: evidence from 70 studies (article). Int J Paediatr Dent. 2018;28(2):170–9.

Further Readings

Crawford PJM, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. Orphanet J Rare Dis. 2007;2:17.
Schüler IM, Haberstroh S, Dawczynski K, Lehmann T, Heinrich-Weltzien R. Dental caries and developmental defects of enamel in the primary dentition of preterm infants: case-control observational study. Caries Res. 2018;52:22–31.
Schwendicke F, Elhennawy K, Reda S, Bekes K, Manton DJ, Krois J. Global burden of molar incisor hypomineralization. J Dent. 2018;68:10–8.
Timothy Wright J, editor. Craniofacial and dental developmental defects - diagnosis and management. Springer; 2015. ISBN 978-3-319-13056-9, ISBN 978-3-319-13057-6 (eBook).
Zhao D, Dong B, Dandan Y, Ren Q, Sun Y. The prevalence of molar incisor hypomineralization: evidence from 70 studies. Int J Paediatr Dent. 2018;28:170–9.

Oral Cancer

Jose Leopoldo Ferreira Antunes, Tatiana Natasha Toporcov, Maria Gabriela Haye Biazevic, and David I. Conway

Contents

11.1 Introduction – 194

11.2 Measurement of the Disease Burden of Oral Cancer – 195

11.3 Standardization or Adjustment of Rates – 197

11.4 Measuring the Global Burden of Disease (Descriptive Epidemiology) – 197

11.4.1 Survival (or Time-to-Event) Studies – 198

11.4.2 Quality of Life Studies – 199

11.5 Assessing Associated Factors (Analytic Epidemiology) – 200

11.5.1 Tobacco Smoking and Alcohol Drinking Are Major Risk Factors – 200

11.5.2 Sociodemographic Characteristics Are Major Determinants – 201

11.5.3 Eating Habits Also Relate to Cancer Risk – 201

11.5.4 Occupational Exposures – 202

11.5.5 Oral Hygiene and Dental Status – 202

11.5.6 Human Papillomavirus (HPV) in Oropharyngeal Cancer – 203

11.5.7 Interaction and Mediation Between Risk Factors – 204

11.6 The Effectiveness of Health Services – 204

References – 206

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_11

Learning Aims

- To depict epidemiology as a potent tool to study "oral cancer" in terms of etiology, prevention, diagnosis, treatment, and rehabilitation
- To measure and to discuss the burden of oral cancer in the population, as regards morbidity, mortality, health-related quality of life, and endpoint treatment outcomes
- To identify the main demographic, socioeconomic, environmental, and behavioral factors associated with oral cancer
- To appraise the effect of health services in preventing oral cancer, diagnosing, treating, and rehabilitating its patients

11.1 Introduction

"Oral cancer" is a comprehensive category of localization for neoplasm and includes tumors of different etiologies and histological profiles, although mostly it refers to squamous cell carcinoma affecting the oral cavity and the oropharynx. Its etiology is multifarious and comprises endogenous factors, such as genetic predisposition, and exogenous environmental and behavioral factors. The disease mostly affects individuals over 45 years of age and, internationally, there is a lot of inter- and intra-regional variation in incidence and mortality [1]. This chapter will review oral cancer definitions, disease burden, and risk factors.

Moore et al. [2] noted the diversity in terms and definitions of oral cancer used in research and epidemiology. These terms include oral cancer, mouth cancer, intra-oral, buccal, and oral cavity cancer. When referring to oral cancer, studies often exclude tumors of the salivary glands. Other anatomical subsites of the mouth (inner and outer surfaces of the lips, gingiva, the floor of mouth, mucosa of the cheek, mouth vestibule, tongue, palate, and retromolar area) are irregularly included. Oral cavity cancer and oropharyngeal cancer are often grouped under the generic term "oral cancer." Classifying the tumors according to their histological classification has also been considered [3].

Epidemiological studies should define unmistaken diagnostic criteria. Researchers should clearly state which topographies their study encompasses, taking into consideration the multiplicity of classification schemes used in the epidemiologic assessment of the disease. Conway et al. [4] proposed a standardized definition of what is oral cavity cancer (tumors affecting the lips, dorsal surface of tongue, gum, floor of mouth, palate, uvula, and cheek mucosa) and what is oropharyngeal cancer (base of tongue, lingual tonsil, tonsil, anterior surface of epiglottis, lateral wall of oropharynx, Waldeyer's ring). A clear distinction between mouth cancer and throat cancer became even more justified after the steep increase in HPV-associated oropharyngeal cancer [5]. HPV-positive oropharyngeal squamous cell carcinoma has been considered an entirely distinct disease entity from HPV-negative squamous cell carcinoma, which affects both the oral cavity and the oropharynx, concerning prognosis, risk factors, and treatment outcomes [6].

Table 11.1 illustrates the classification schemes used by some epidemiological studies. The selection of

Table 11.1 Classification schemes of tumor sites in some studies on oral cancer

Author, year	Provenance	Oral cancer sites
Pindborg, 1977 [8]	Several countries	Lips, tongue, oral cavity
Smith et al., 1990 [9]	Several countries	Lips, tongue, oral cavity, salivary glands, tonsil, oropharynx, nasopharynx, hypopharynx
Kleinman et al., 1993 [10]	Several countries	Lips, tongue, oral cavity
Swango, 1996 [11]	EUA	Lips, tongue, oral cavity, salivary glands, tonsil, oropharynx, nasopharynx, hypopharynx
O'Hanlon et al., 1997 [12]	Northwest, England	Tongue, oral cavity
Moore et al., 2000 [13]	Several countries	Lips
Antunes et al., 2001 [14]	Sao Paulo, Brazil	Lips, tongue, oral cavity
Toporcov et al., 2004 [15]	Sao Paulo, Brazil	Lips, tongue, oral cavity, tonsil, oropharynx
Komolmalai et al., 2015 [16]	Thailand	Lips, tongue, oral cavity
Ong et al., 2017 [17]	Leeds, England	Lips, tongue, oral cavity
ThekkePurakkal et al., 2018 [18]	Kerala, India	Tongue, oral cavity, tonsil
Monteiro et al., 2018 [19]	Portugal	Lips, tongue, oral cavity, tonsil, oropharynx

Table 11.2 Correspondence of codes for oral cancer sites, International Classification of Diseases, ninth, tenth, and eleventh revisions

Anatomic subsites	ICD-11	ICD-10	ICD-9
Lips	2B60	C00	140
Tongue	2B61 and 2B62	C01 and C02	141
Gum	2B63	C03	143
Floor of mouth	2B64	C04	144
Palate	2B65	C05	145.2–145.5
Salivary glands	2B67 and 2B68	C07 and C08	142
Tonsil	2B69	C09	146.0–146.2
Oropharynx	2B6A	C10	146.3–146.9
Other or unspecified parts of the mouth	2B66	C06	145.0, 145.1, and 145.4–145.9
Other or ill-defined sites in the lip, oral cavity, or pharynx	2B6E	C14	149

Source: ► https://icd.who.int and International Classification of Diseases for Oncology (ICD-O), 3rd edition [7]

papers did not follow any criteria; the purpose was solely showing different choices over time. Table 11.2 explains the anatomical locations usually considered in the topographic classification of oral cancer, based on the correspondence between the ninth, tenth, and eleventh revisions of the International Classification of Diseases [7].

11.2 Measurement of the Disease Burden of Oral Cancer

► Box 11.1 synthesizes measures of disease burden. These measures can be stratified and standardized by age, sex, and geographic area (e.g., urban and rural), or area-based socioeconomic classification.

Box 11.1 How to Measure Oral Cancer Disease Burden

Mortality

Mortality rates due to oral cancer or cancer in different sites of the mouth are the quotient between two quantities. The numerator is the number of deaths caused by oral cancer in general, or by tumors in specific subsites of the mouth, which occurred in a specified area and period. The denominator is the population of the same area in the middle of the period.

Proportional Mortality Ratio

It refers to the number of deaths due to a specific cause divided by the total number of deaths within a specific population, during a period. The proportion of cancer deaths in the general mortality in a given area and period may be of interest, or the percentage of deaths due to oral cancer among the total cancer mortality.

Prevalence

It encompasses all existing cases of the disease, irrespective of being new cases or previously existing ones. The prevalence is the quotient between the number of existing cases (new and old) in a given area and period, divided by the population of the same area, in the middle of the period.

Prevalence is easy to assess; it is the only measure of disease occurrence that can be assessed by cross-sectional surveys. In cancer epidemiology, however, its usefulness is limited by the indefinite duration of each case.

Incidence

It relates to the number of new cases of a disease, which started during a given period. The incidence is more difficult to assess; it depends on an institutional scheme (population-based or hospital-based cancer registry) to gather longitudinal information on any new case, as soon it occurs and is diagnosed.

The incidence rate is the number of new cases in a specified area and period, divided by the population at risk of the same area, in the middle of the period. The cumulative incidence (or incidence proportion) refers to the risk of an outcome and is the number of new cases that occur in a specific area during a follow-up period, divided by the closed population initially at risk. The incidence density rate is the number of new cases divided by the population initially at risk and the time of follow-up.

Incidence is the best measure of cancer burden related to risk. It reflects the flow of new cases arising from the

population, irrespective of the duration of the disease or any other treatment outcome.

Proportional Morbidity
Concerning morbidity indicators (incidence and prevalence), it may be of interest to assess the percentage of cases of oral cancer among all malignant neoplasm cases. This proportion uses two different denominators: total cancer cases and the same total, excluding skin cancer, except melanoma. This differentiation may be useful in many cases, since skin neoplasm (except melanoma) have unique epidemiological characteristics, such as high incidence and low mortality.

Case Fatality Rate
It assesses disease severity, instead of the frequency of cases. The assessment of disease severity can also use sequela, complications, absenteeism, impact on quality of life, expenditures, and so forth. Anyhow, it is quite useful to consider the fatal outcome of disease as a condition of extreme severity. The case fatality rate is the relation between the number of deaths due to a specific disease, among cases occurred in a specific area and period.

Ideally, this definition refers to prospective studies because a cohort of patients has to be followed up during a specified period, thus quantifying how many died and how many survived. However, another measurement has been defined to allow a more straightforward assessment, the mortality to incidence ratio (MIR), merely dividing these two rates for a specific area and period [20].

Survival Analysis
It refers to another class of longitudinal studies, which begins with the enrollment of patients according to a clear case definition. This group will be followed up prospectively during a specified period after diagnosis, registering how many died from the disease, how many died from other causes, and how many are still alive. A class of statistical procedures allows comparing the association of survival and exposures such as sociodemographic conditions, clinical status, behavior, and access to health facilities.

11

Cancer surveillance uses data from vital statistics, risk factor surveys, and population-based cancer registries. The primary source of incidence data is the population-based cancer registry. However, many cities do not notify cancer cases to the health authorities on a regular basis; others do not do it at all. Cancer registries are widespread in high- and middle-income cities and countries; many of them provide reliable and comprehensive time series information on incidence, which are synthesized by the International Association for Research on Cancer (IARC) in the series "Cancer Incidence in Five Continents." [21] Hospital-based cancer registries are also useful to assess information on prognosis, such as survival.

Worldwide, several cities and countries have population-based cancer registries, and the World Health Organization (WHO) and the IARC provide systems depicting international data on cancer incidence and mortality, such as GLOBOCAN, and the "European Health for All" family of databases. The Global Cancer Observatory (GCO) is an interactive web-based platform (► http://gco.iarc.fr/) depicting global cancer statistics. Maintained by the IARC, the platform focuses on the epidemiological profile of the disease worldwide, using data from GLOBOCAN and several other databases on incidence and mortality.

The Global Cancer Observatory gathers the data collected in each country and collaborates with national staff to improve local data quality and coverage. In Brazil, the National Cancer Institute [22] reported the existence of cancer registries in 21 cities in 2011. Subsequently, the federal law N. 13,685 (June 2018) included cancer in the list of notifiable diseases, giving rise to expectations of making possible to monitor information of all new cases of cancer throughout the country shortly.

Explicitly referring to information on mortality, the IARC also provide access to the WHO cancer mortality database (► http://www-dep.iarc.fr/WHOdb/WHOdb.htm). However, differential standards of data quality and coverage also affect mortality databases. Poorer regions can incur in underreporting of deaths. Also, deaths of older individuals may miss the determination of the underlying cause in areas or countries submitted to deprivation and limited health services. Older individuals can have restricted locomotion and access to diagnosis and treatment. Moreover, under material deprivation and insufficient provision of health services, underlying causes of death would not be extensively investigated for the elderly, a factor described as likely to affect cancer statistics [23] and general mortality [24].

Some epidemiological studies, such as the Global Burden of Disease (GBD) [25] study, considered this limitation when focusing on mortality estimates and developed analytical schemes to redistribute deaths by unspecified and ill-defined causes [26]. Beginning at the 1990s, the GBD is an international effort to compile systematic evidence quantifying the impact from diseases, injuries, and risks on specified populations over time. The GBD study developed a tool providing public access to cancer statistics worldwide: ► http://ghdx.healthdata.org/gbd-results-tool

Prevalence data on cancer in general, and on oral cancer in particular, are less used, due to technical difficulties. It is not feasible to estimate cancer prevalence accurately from sample data, as epidemiologic surveys usually do for more common oral diseases, such as dental caries and periodontitis. Nonetheless, National Health Surveys conducted worldwide usually assess self-reported information on cancer prevalence during the lifetime.

The assessment of cancer prevalence has additional limitations. It is difficult to monitor and control which cancer cases have not resulted in cure or death in each period. However, when the specific assessment of prevalence is required, for instance, to instruct some health program aimed at patients, the indirect estimation of the total number of cancer patients (including old cases) is possible; using analytical schemes based on the incidence, duration, and estimated patient survival [27].

11.3 Standardization or Adjustment of Rates

Incidence and mortality rates are quotients between two counts (the number of the event and the number of inhabitants at risk), which estimate the risk of events. For the oral cancer mortality rate, for example, the event of interest is of dying from this disease. This result is referred to as gross or non-adjusted when its calculation does not consider factors that may interfere with the risk of the disease, such as the distribution of population by sex and age group. Non-adjusted rates are used to assess the burden of disease and can instruct health services in the planning of resource allocation.

However, the distribution of population by sex and age group influences both the risk of incidence and mortality by cancer. Therefore, unadjusted rates do not allow comparisons between contexts that differ in population structure. Epidemiologic studies on cancer risk usually require comparisons across time and space (within and between countries), thus reinforcing the need for adjusting the rates.

For physiologic and behavioral reasons, some diseases affect women more than men; others have the opposite direction. Susceptibility to some infectious diseases is higher among children; other diseases affect adults more intensely, such as cardiovascular diseases, which depend on the cumulative effect of long-term exposure to risk factors.

The standardization or adjustment of cancer incidence and mortality allows obtaining risk estimates that can be compared between populations at different times or allocated in different geographic areas, irrespective to the fact that their population structures differ in age and sex distribution.

The direct standardization is a weighted average of the sex- and age-specific rates, using as weights the external reference of the standard population. The adjusted rate is the result of the following formula. The sex- and age-specific rates are "r_i" and "p_i" are the respective weights assigned to each of the "i-th" sex and age groups.

$$\text{Adjusted rate} = \sum_{i=1}^{n} p_i \times r_i$$

The quotient between the number of events (cases or deaths) by the number of inhabitants in each sex and age-group gives the values of "r_i". The "p_i" corresponds to the relative frequencies of each group (sex or age) in the standard population. If the adjustment is only for sex, n is two, and the groups refer to women and men in the population. If adjustment is only for age, n is the number of age groups. If the adjustment is concurrently for sex and age, the number of groups is the double of the previous condition, thus gathering all age groups in each sex.

This method requires selecting an appropriate standard population. The Union for International Cancer Control (UICC) discussed the proposition of a standard population in May 1965 in London [28]. One of the proposals took the "European population" as a reference and resulted in a higher proportion of older individuals [23]. Segi et al. [29] proposed other distribution (the world population), summing up the population of 46 countries, circa 1950. Table 11.3 depicts these standard populations together with a reference subsequently prepared by a WHO working group to update the old propositions [30], which attempted to reflect more accurately the contemporary average pattern of age distribution worldwide.

11.4 Measuring the Global Burden of Disease (Descriptive Epidemiology)

The WHO and the IARC regard oral cancer as the most frequent neoplasm affecting the head and neck, with an estimated 529,000 new cases and 292,000 deaths worldwide in 2012. The World Cancer Report 2014 depicted country-specific times series for the incidence, showing higher rates in Slovakia and India, increasing trend in Denmark, Uganda, and Japan, and a decrease in China, Australia, and the United States [31].

Stanford-Moore et al. [32] observed that tobacco smoking and alcohol drinking had a steeper effect on the risk of head and neck cancer for population groups earning lower income and with lower educational level. Faggiano et al. [33] gathered evidence on the association between cancer epidemiologic indices and social development in several countries. Although the assessment of

Table 11.3 Standard population distribution (percent), for adjusting rates

Age group	World population	European population	WHO world population
0–4	12.00	8.00	8.86
5–9	10.00	7.00	8.69
10–14	9.00	7.00	8.60
15–19	9.00	7.00	8.47
20–24	8.00	7.00	8.22
25–29	8.00	7.00	7.93
30–34	6.00	7.00	7.61
35–39	6.00	7.00	7.15
40–44	6.00	7.00	6.59
45–49	6.00	7.00	6.04
50–54	5.00	7.00	5.37
55–59	4.00	6.00	4.55
60–64	4.00	5.00	3.72
65–69	3.00	4.00	2.96
70–74	2.00	3.00	2.21
75–79	1.00	2.00	1.52
80–84	0.50	1.00	0.91
85+	0.50	1.00	0.60

Source: Ahmad et al. [30]

oral and pharyngeal cancer incidence did not reveal a clear socioeconomic gradient, mortality data for men showed deprived populations to have an excessive burden of the disease in practically all the countries studied. This observation raises the hypothesis that socioeconomic status can influence the outcomes of cancer treatment and access to adequate healthcare [34].

Studies assessing the burden of disease should focus not only on the overall association of incidence and mortality with socioeconomic indices but also on the absolute and relative inequality affecting socioeconomic strata [35]. This information is of foremost importance for health promotion and healthcare planning.

The concept of "burden of disease" [36] refers to a comprehensive assessment of the impact of disease on population and can be estimated by multiple measures. A higher disease burden, concerning cancer, can be inferred by different conditions, such as morbidity and mortality indices; disability acquired as a result of the disease; financial costs related to treatment and inability. Explicitly referring to cancer, other conditions implies a higher disease burden: the risk of incidence of avoidable types; the late diagnosis of detectable neoplasm by screening during early stages; inappropriate or absent healthcare; the risk of death from cancer types that are usually curable; not receiving the necessary resources for the control of pain and other palliative care.

The GLOBOCAN project (▶ http://globocan.iarc.fr), maintained by the WHO and IARC, provides observed data and contemporary estimates of cancer epidemiologic indices (incidence, prevalence, and mortality) from the main types of cancer, at the country level. According to information depicted by this project, Papua New Guinea had the highest incidence of oral cavity and lip cancer in males (age-standardized rate estimated for 2012): 30.3 new cases per 100,000 inhabitants. With figures ranging from 10.1 to 13.0 Bangladesh, Kazakhstan, Pakistan, and India were also among the highest rates. In Europe, the highest rates affected Hungary, France, Portugal, and Romania (10.0 to 15.7). Australia (8.8), Russia (8.5), the United States (7.5), and Brazil (7.2) ranked median rates in the worldwide distribution. Italy and Sweden (4.1), Japan (3.9), Colombia (3.3), Mexico (3.1), and Greece (2.3) ranked among the lowest rates.

Studies on the burden of oral cancer assess the incidence and mortality attributed to the disease. Shield et al. [37] described the incidence of lip, oral, and pharyngeal cancers worldwide, as stratified by sex, country, and subsite, using GLOBOCAN data. They concluded that the rising incidence of these tumors and their variation across the countries justified the demand for locally tailored approaches to prevention and treatment programs. This type of study also involves the assessment of trends in the distribution of the disease in distinct geographic units, such as small areas or neighborhoods within a city, or towns within a country. Chaturvedi et al. [38] reported the rising trend in the incidence of oropharyngeal cancer trends in many developed countries, mostly involving adults aged less than 60 years, and interpreted this result as compatible with the hypothesis of HPV infection. They also concluded that the burden of oral cavity cancer remains even higher in many parts of the world, thus underscoring the importance of strategies targeted toward the reduction of tobacco and alcohol consumption.

11.4.1 Survival (or Time-to-Event) Studies

The prospective monitoring of patients with oral cancer can inform the assessment of survival and associated factors. Survival (or time-to-event) studies are a specific modality of cohort studies, in which having the disease is an inclusion criterion, and the outcome is the time for an event. The event of interest can be death due to the disease, tumor recurrence, hospital discharge, or any

other endpoint result of interest in the assessment of disease burden. When survival refers to remaining alive, a usual way to describe results is to depict the proportion of survivors after 5 years of the initial diagnosis. Statistical analysis uses specific techniques for the dimensioning of risk factors for death.

For carcinoma at the head and neck, cancer staging influences the prognosis importantly. In general, larger tumor size and its capability of spreading metastasis to regional lymph nodes are the most relevant markers of biological aggressiveness [39]. The emergence of HPV-related oropharyngeal cancer led to the acknowledgment of a different epidemiologic profile, with a superior survival compared to patients with HPV-unrelated oropharyngeal cancer. This observation accounts for the proposition of a new clinical staging system in case of tumors associated with HPV infection [40].

An example of this type of research, Carvalho et al. [41] evaluated changes in the prognosis of oral and oropharyngeal cancer patients treated at a hospital in Brazil from 1953 to 1997. The follow-up of 3267 patients over almost five decades showed an increased survival rate. An increased proportion of patients undergoing surgical treatment and surgery in combination with radiotherapy influenced this improvement. The final, adjusted statistical model highlighted the characteristics associated with a higher risk of death. These characteristics were male sex, age 65 or older, posterior localization of the tumor, and advanced clinical stage, as classified by the TNM staging system [42], referring to the assessment of the size of the Tumor, the involvement of regional lymph Nodes, and the spread to other parts of the body by distant Metastasis.

As another example of a study assessing the time to an event, Gandara-Vila et al. [43] followed up 85 patients affected by oral leukoplakia, a potentially malignant condition, for up to 11 years. They observed that seven patients developed oral carcinoma, and they concluded that, in their sample, the presence of dysplasia was the only risk factor statistically associated with malignant transformation.

11.4.2 Quality of Life Studies

"Quality of life" and "health-related quality of life" are practical outcomes to assess oral cancer disease burden. These concepts have been increasingly used in studies evaluating health conditions and the impact of disease and therapeutic applications in patients with different diseases. For oral cancer patients, in particular, the appraisal of the self-reported quality of life of patients is an implement to assess the effectiveness of treatments.

Despite recent advances in diagnosis and treatment, oral cancer continues associating with facial disfigurement and dysfunction in critical life domains, such as speech, taste, chewing, and swallowing. In addition to contributing to the monitoring of treatments, assessments of quality of life enable health professionals to understand how patients experience the evolution of the disease and the consequences of treatments such as surgery and radiotherapy.

In 1994, a WHO working group proposed a definition for the concept of quality of life that was both transcultural and nonspecific for any single disease:

> » Quality of life is a persons' perception of his/her position in life within the context of the culture and value systems in which s/he lives and in relation to his/her goals, expectations, standards, and concerns. It is a broad-ranging concept incorporating, in a complex way, the person's physical health, psychological state, level of independence, social relationships, personal beliefs, and relationships to salient features of the environment. [44]

The WHO working group considered that previous attempts to assess the quality of life failed to include all relevant dimensions and were not sufficiently reliable [45]. Subsequently, however, this branch of knowledge underwent an intensive development, and many new data-gathering tools tried to address all domains potentially related to the quality of life. Several questionnaires focused on oral health-related quality of life and gathered information about the perception of impacts caused by dental conditions.

Two comprehensive questionnaires aimed at patients with head and neck cancer are the most widely used worldwide: the UW-QOL and the QLQ-H&N35.

The UW-QOL (University of Washington Quality of Life questionnaire) appraises the impact of the disease and associated treatments on 12 domains of the quality of life: pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, mood, and anxiety [46]. In addition to the domain-specific assessment of the quality of life, the UW-QOL contains three general questions, with response alternatives in the form of a scale, and an additional multiple-response question on which functions were the most strongly affected. Quality of life outcomes, as informed by the UW-QOL, can instruct multiple comparisons by sex, age group, TNM classification, anatomical location of the tumor, type of treatments, recurrence, and sequela.

The European Organization for Research and Treatment of Cancer (EORTC) developed the QLQ-H&N35 (the acronym stands for "Quality of Life Questionnaire – Head and Neck, 35 questions"), aiming to assess the quality of life of patients with head and neck cancer in the international context. The 35 questions encompass several domains of health-related qual-

ity of life (pain, soreness, swallowing, teeth, mouth opening, cough, and others.), which refer to the precedent week [47]. Thirty questions offer four options as answers (not at all, a little, quite a bit, and very much); the remaining five questions solely offer yes or no. The EORTC recommends converting these answers into a linear scoring scale, with values ranging from 0 to 100.

In an example of studies on quality of life, Melissant et al. [48] reported a reduction of sexual interest and enjoyment in patients with head and neck cancer, treated with chemo or radiotherapy with curative intent in the Netherlands. Patients responded to the EORTC questionnaire (QLQ-H&N35) several times during a 24-month prospective follow-up. Results showed a significant increase in the proportion of patients reporting less sexuality from the baseline (before starting the treatment) to the six-week follow-up, with differences in scores losing statistical significance from the 12-month follow-up onwards. Less sexuality over the time was related to female gender and poor social functioning.

Biazevic et al. [49] analyzed the immediate impact of primary surgery in patients with oral and oropharyngeal cancer, by comparing scores obtained previously and shortly after the surgery. Chewing, tasting, and swallowing were the most affected domains. Only anxiety improved at this stage of treatment; patients felt relieved and optimistic after tumor excision. Among survivors, significant functional limitations persisted 1 year after surgery [50]. Both the one-year follow-up and the assessment of immediate impact used the Brazilian Portuguese version of the UW-QOL questionnaire [51].

Quality of life information is an essential adjunct to the assessment of clinical outcomes. Healthcare providers should engage in gathering the self-report of patients on how they experience disease and treatment. For patients with oral cancer, information on the quality of life helps to identify those in need of additional supportive care. Epidemiologic research on health-related quality of life is valuable to instruct the planning and implementation of treatment protocols.

11.5 Assessing Associated Factors (Analytic Epidemiology)

A dynamic quest of etiological and associated factors for oral cancer is ongoing in the literature. For head and neck cancer in general, and for oral cancer in particular, tobacco smoking and alcohol drinking are the major risk factors, as confirmed by the International Head and Neck Cancer Epidemiology (INHANCE) consortium [52, 53]. Involving nearly 25,500 patients and 37,100 controls gathered in 35 case–control studies worldwide, this international initiative has actively conducted large epidemiologic studies about the causes and mechanisms involved in head and neck cancer [54].

A low frequency of intake of fruits and vegetables has also been consistently reported as a risk factor [55, 56]. Pooled analyses of studies participating in the INHANCE showed that poor socioeconomic status (education and income) associated with head and neck cancer independent of differences in tobacco smoking and alcohol drinking across socioeconomic strata [54].

Age and gender distribution are also the main determinants of oral cancer distribution and must be taken into consideration as adjusting factors in studies assessing factors that associate with the disease. Other risk factors currently assessed include use of mouthwash, inherited conditions (family history of head and neck cancer), short height, and lean body mass [54].

11.5.1 Tobacco Smoking and Alcohol Drinking Are Major Risk Factors

The IARC stated that the use of tobacco and the exposure to involuntary smoking do cause oral cancer and other neoplasms. Tobacco smoke has many chemical agents and compounds that are carcinogenic, and the frequency and duration of the habit are directly related to the risk of disease [57]. The Framework Convention on Tobacco Control, maintained by the WHO, is an initiative to consolidate the global effort to control the use of tobacco and its deleterious effects on human health. More than 180 countries joined the initiative (► http://www.who.int/fctc/en).

Alcohol drinking is an independent risk factor for oral, pharyngeal, esophagus, and laryngeal cancer [57, 58]. Furthermore, alcohol interacts synergistically with tobacco in increasing the risk of these neoplasms. An "alarming" rise in oral cancer among adults in their 40s, in the United Kingdom, was attributed to the increase in alcohol consumption by adolescents and young adults [59]. These observations are consistent with the persistence of a higher risk of the disease among men than among women, as the prevalence of alcohol consumption at levels potentially harmful to health is higher for men [60].

The quest for causes must consider the already known risk factors and the differences in incidence between the genders, age groups, and social strata [31]. Studies on the effect of new exposures should include these characteristics as adjusting factors in the statistical models. The contemporary agenda of oral cancer epidemiologic research has focused on more subtle risk factors, and interactions and intermediations between covariates of interest.

11.5.2 Sociodemographic Characteristics Are Major Determinants

Social inequalities affect the distribution of oral cancer. Several studies have reported the lack of equity in the distribution of disease burden and the association between its epidemiologic indices and measures of socioeconomic status. A systematic review encompassing case–control studies performed worldwide concluded that the risk of oral cancer persisted unequally distributed across socioeconomic strata, as referred to categories of income, education, and occupational class [61].

The study of the association between oral cancer and social deprivation is complex and suggests different possibilities. On the one hand, poor living and working conditions may associate with more intense exposure to risk factors. On the other hand, the social stratification of the disease may also reflect differential patterns of access to health information and services. In general, deprived individuals receive less health information, are less susceptible to behavior change, have less therapeutic resources, and lower access to early diagnosis and poorer prognosis when affected by the disease.

Tomatis [62] stated that the knowledge already available on cancer etiology has not enabled a substantial reduction in incidence among deprived populations. Furthermore, the survival period of cancer patients in developing countries would be about one-third of that observed in developed countries.

An effort to interpret the impact of socioeconomic inequality on oral cancer should consider the differential prevalence of risk factors among social groups. In studying the links between socioeconomic status and epidemiologic indices of oral cancer, O'Hanlon et al. [12] pointed out material deprivation as a possible factor for relevant changes in the prevalence of harmful behaviors, such as tobacco smoking and alcohol drinking. Puigpinós et al. [63] also considered this argument to explain their result of stationary absolute and relative inequalities in mortality by mouth and pharynx cancer across the educational strata. A large case–control study (the Carolina Head and Neck Study [32]) specifically assessed the interaction between socioeconomic status and behavioral factors, showing that the socioeconomic gradient was more pronounced for current tobacco smokers and current alcohol drinkers than for their never-smoker and never-drinker counterparts.

In Sao Paulo, the largest city in Brazil, oral cancer mortality was higher in neighborhoods with lower average income and education, and higher unemployment and illiteracy rates, reinforcing the perception of disparities in the distribution of the disease [14]. In addition to having lower death rates, richer vicinities had decreasing trends of oral cancer mortality, whereas the inverse occurred in impoverished areas. This finding suggests that inequalities in the experience of the disease may be on the rise.

A subsequent study in the same city [64] reported gender and racial inequalities in oral cancer mortality. Although death rates were stationary for whites, they doubled in a few years for blacks. Also, an increasing trend of death rates for women was in contrast with the stationary trend observed for men. The surveillance of unfair, avoidable, and unnecessary inequalities in health outcomes across gender, racial, and socioeconomic strata may contribute to implementing socially appropriate programs and policies, concurrently aiming to reduce the burden of disease and promote social justice.

The relationship between socioeconomic status and survival of patients with oral cancer is worth mentioning. The monitoring of survival of more than 3600 patients with oral cancer in Taiwan showed that those from poor neighborhoods had between 1.46 and 1.64 higher mortality in 2 years than those residing in areas with higher income and number of doctors [65].

11.5.3 Eating Habits Also Relate to Cancer Risk

Assessing dietary factors in observational studies on cancer risk is a challenging task. Heterogeneous farming and growing techniques may influence the consistency of the findings, interfering in the comparison of results obtained in studies assessing different regions. Cultural aspects of food preparation also entail the possibility of confounding. Memory bias may affect the recollection of eating habits before diagnosis and is a considerable limitation of case–control studies. Furthermore, some food items are consumed in high correlation with other ones, thus demanding a complex assessment of eating patterns, rather than specific food items.

The WHO estimates that 15–35% of all cancer cases are likely related to nutritional standards, such as low intake of fruits, vegetables, and micronutrients, or excessive consumption of proteins, fats, carbohydrates, preservatives, and additives [31]. This information led to the proposition of administering micronutrients and other nutritional strategies for primary and secondary chemoprevention of cancer [66]. Citric juices and dietary fibers can also contribute to cleanse the mouth and mechanically remove potentially carcinogenic substances in contact with oral mucosa [15].

The assessment of dietary habits as risk factors for head and neck cancer, in general, has been dynamic within the INHANCE consortium. Chuang et al. [55] confirmed the protective effect of frequent intake of

fruit and vegetables, and the deleterious association with red meat. Galeone et al. [67] reported a possible moderate inverse association between garlic and onion intake and HNC risk; Kawakita et al. [68] confirmed the hypothesis that a higher intake of dietary fiber might reduce the risk of disease.

As an example of a study addressing a specific hypothesis on micronutrients, Galeone et al. [69] reported a strong inverse association between folate (vitamin B9) intake and oral cavity cancer, in a study including thousands of patients in different countries. The food frequency questionnaire considered the intake of foods rich in folate (green leafy vegetables, legumes, cereals, and fruits, fortified food products, and supplements with folic acid).

As an example of a study assessing the hypothesis that diet exerts local effects on oral mucosa, Toporcov et al. [70] assessed the putative protection of the frequent intake of fruits and salads, analyzing how this effect differed between smokers and nonsmokers, and between alcohol drinkers and nondrinkers. The cleansing of oral mucosa by the frequent intake of fresh fruits and vegetables might reduce the absorption of carcinogenic substances present in tobacco. They concluded that dietary fiber, citric juices, and oligosaccharides from fruits might clean oral mucosa and help to prevent the carcinogenic effects of tobacco and alcohol consumption.

Epidemiological studies on diet and oral cancer have also assessed other hypotheses. A study carried out in the city of Sao Paulo concluded that daily coffee consumption associated with a lower risk of oral squamous cell carcinoma. The conceptual framework guiding the fitting of the model allowed adjusting the associations for the deleterious effect of behavioral exposures (tobacco, alcohol, and other dietary habits), the inverse association between the disease and income, and the differences across gender and age groups [71]. The hypothesis of a protective effect for coffee intake is not straightforward; indeed, the authors summarized previous evidence pointing out to conflicting conclusions. Subsequently, however, a systematic review reinforced the perception that coffee protects against oral and pharyngeal cancer [72].

Another meta-analysis assessed tea consumption and oral cancer [73]. The concurrent appraisal of 19 studies concluded that the highest category of overall tea consumption was protective against oral cancer both for Asian and Caucasian populations. This effect was even more noticeable in the specific assessment of green tea and nonstatistically significant for black tea. Authors attributed this result to different constituents in each type of tea.

Still referring to this theme, a systematic review summarized the higher odds of oral and oropharyngeal cancer among maté drinkers, a common beverage in Latin America [74]. Authors concluded that evidence up so far available could not determine whether this observation is due to maté's carcinogenic constituents or the very high temperature it is usually served.

11.5.4 Occupational Exposures

Regarding occupational risk factors for oral and pharyngeal cancer, Boing et al. [75] pointed out the higher risk of the disease among workers with a low professional qualification (manual workers) in comparison with their better qualified (nonmanual workers) counterparts. Authors attributed this difference to socioeconomic inequalities in this outcome and observed that the higher risk of non-skilled workers remained statistically significant after adjusted for the cumulative exposure to tobacco smoking and alcohol drinking during the lifetime.

The contribution of cumulative ultraviolet radiation to carcinogenesis in cutaneous tissue is well understood. Specifically for lip cancer, the frequent exposure to sunlight has been assessed as a contributing factor to increasing the risk of the disease. This factor affects, in particular, those working in the external environment, such as dock workers, seamen, farmers, fishers, and construction workers [13, 76].

Some industrial activities subject the workers to the exposure to asbestos and other chemical substances that are recognized or suspected to be carcinogens [31, 58, 77]. A large case–control study conducted by the IARC (the ARCAGE – Alcohol-Related Cancers and Genetic-susceptibility in Europe study [78]) assessed occupational risk factors for cancers of the upper aerodigestive tract. Professional categories related to construction (painters; bricklayers, stonemasons and tile settlers; civil engineers; workers in the general construction of buildings, roads, and motorways) had significantly higher odds of oral and oropharyngeal cancer.

11.5.5 Oral Hygiene and Dental Status

The literature raised several new hypotheses on the possible effects of oral hygiene and dental status on the risk of oral cancer. Studies implicating the low frequency of tooth brushing in oral carcinogenesis ruled out the hypothesis that insufficient control over intervening or confounding factors could explain this association [79, 80]. One of the hypotheses considered was the potential contribution of tooth brushing, when frequent and regular, in removing or diluting carcinogenic substances present in the mouth and, thus, preventing oral cancer. Authors also suggested that this result was due to the

mechanical removal of pathogens present in the oral microbiota, which could exert some deleterious action. Species of *Candida*, *Neisseria*, and *Streptococcus* could act both in the production of nitrosamines and in the conversion of ethanol to acetaldehyde. Anyhow, the link between microorganisms and oral cancer is still inconclusive [81] and deserves further investigation.

The literature has also raised the hypothesis that periodontal disease may somehow associate with the risk of oral cancer [82]. The stimulation of chronic inflammation and the influence of bacteria on the cell cycle through the promotion of cell proliferation and inhibition of apoptosis may contribute to explain the possible participation of microbial species related to periodontitis in the risk of oral cancer.

The epidemiologic assessment of this hypothesis is not an easy task, because both cancer and periodontal disease are chronic conditions, and they share common risk factors as alcohol and tobacco. Even so, some studies have approached the theme. Yao et al. [83] conducted a systematic review and meta-analysis and retrieved just five studies, which supported the hypothesis that patients with periodontitis were more susceptible to oral cancer. Michaud et al. [84] used the number of teeth as a surrogate marker of periodontitis and concluded that the existing evidence supported the association between periodontal disease and the risk of oral, lung, and pancreatic cancer.

The frequent use of mouthwash has also been assessed as a possible risk factor for oral cancer, due to its non-negligible alcohol content. Guha et al. [85] concluded that the daily use of mouthwash is an independent cause of cancers of the head and neck, and esophagus. Osso and Kanani [86] concluded contrariwise that mouthwash use does not increase the risk of oral cancer. Based on data obtained in the ARCAGE study, Ahrens et al. [87] concluded differently that the effect of alcohol content in most formulations of mouthwash remains to be fully clarified.

Notwithstanding discrepant results, the possible association between mouthwash use and oral cancer is complex and difficult to assess. Participants would have to focus on previous patterns rather than on the use of mouthwashes after the diagnosis. Researchers would have to consider that some mouthwashes are free of alcohol. Worth mentioning, any result favoring or disfavoring the use of mouthwash may involve commercial interests. Anyhow, this is a subject that indeed demands more investigation.

Recurrent sores of oral mucosa caused by poorly adjusted dental prostheses have also been hypothesized as contributing factors for oral cavity cancer [79, 88]. Studies appraising this hypothesis suggested that the chronic irritation of the epithelium contributed to the topic carcinogenic effect of alcohol and tobacco.

A direct carcinogenic effect of local traumatic inflammation was not considered. However, taking into consideration the carcinogenic effect of tobacco and alcohol in the mouth, what would we think of the continued deposition of these substances on oral soft tissue recurrently hurt by ill-fitting dentures? Exposures do not occur in separate; they accumulate and interact in many people. The use of ill-fitting, hurting dentures is not an uncommon condition among adults and old individuals. Unfortunately, many of them smoke and drink alcohol, and many remain using inappropriate dental prosthetic devices for a long time.

11.5.6 Human Papillomavirus (HPV) in Oropharyngeal Cancer

Specific strains of the human papillomavirus, mainly the HPV 16, have long been acknowledged as a cause of cervical cancer. HPV has also been implicated in carcinogenic processes in other sites, like the anus, vulva and vagina, penis, and oropharynx and tonsil [89]. In the United States, the incidence of cervical cancer decreased by 1.6% per year from 1999 to 2015, while oropharyngeal cancer increased 0.8% per year among women, and more steeply for men (2.7%) [5]. These trends led oropharyngeal squamous cell carcinoma to be the most common HPV-related cancer in the country. Indeed, an assessment of geographic heterogeneity of HPV prevalence in oropharyngeal squamous cell carcinoma had already reported that the problem affects more the United States (60%) than Europe (30%) and Brazil (4%) [90].

Considering the hypothesis that oral sex may be the means by which HPV can infect the oropharynx, a study within the INHANCE consortium reported evidence of a higher odd of oropharyngeal cancer among individuals with four or more lifetime oral sex partners. Also, the odds of cancer in the base of the tongue associated significantly with ever having had oral sex [91].

Epidemiology has much to contribute to the surveillance of HPV-related cancers, and the planning of health interventions aimed at the problem, as the vaccination against HPV. As an example of this type of research, Brouwer et al. [92] compared trends and age effects of oral cancer in the United States, as classified by the localization of the tumor. Justifying this classification, the authors mentioned previous studies that considered the oropharynx and the base of the tongue as sites likely related to HPV infection, and anterior regions of the mouth as unrelated. The incidence of cancer in HPV-related sites ranked higher for younger cohorts and more recent periods, whereas the inverse occurred for HPV-unrelated sites. Considering that the main risk factors – tobacco smoking and alcohol drinking – affect

both the posterior and anterior subsites of the mouth, they concluded that the differences observed were likely due to the spread of HPV.

11.5.7 Interaction and Mediation Between Risk Factors

The epidemiologic assessment of the interaction and mediation between risk factors is a valuable perspective in epidemiology. Interaction and mediation refer to the concurrent assessment of two or more risk factors [93]. The epidemiological interest relies on explaining how different exposures and conditions (genetics, behavior, clinical status, access to treatment, and others) combine their effect on the disease outcome.

Interaction occurs when a factor has its influence on the outcome potentiated or attenuated by the presence of another. Exposures may have their effect amplified, diminished, or otherwise modified when occurring concurrently with another factor. Statistical models including interaction terms involving the product of the factors of interest can gain in explicative purposes.

Mediation also comprises the mutual influence of two or more risk factors. In this case, the analytical interest relies on explaining how much of the influence of a factor is due to the concurrent exposure to another factor, and how much would remain if the other factor had not intervened. Instead of assessing product terms in linear models, the study of mediation involves comparing how much of the effect of a factor is modified when the intermediate variable is included in the model.

As an example of interaction, Antunes et al. [94] compared the independent and joint effects of tobacco and alcohol on oral cancer, in a large case–control study. They observed that including a product term for the concurrent exposure to tobacco and alcohol improved the model's goodness of fit. Furthermore, the inclusion of the product interaction term allowed adjusting the odds ratios for the independent effect of each exposure, giving more reliable estimates of the individual contribution of both alcohol and tobacco to the risk of the outcome. Based upon these results, they also concluded that policies aimed at cancer control should focus on addictive behaviors rather than on single lifestyle risk factors.

In another interesting example of a study on the interaction between two exposures, Chen et al. [95] assessed the association between oral cancer and both the regular intake of milk and tea (black or green), in China. In this case, however, both factors were protective against the disease. However, the protective effect of tea was even stronger among those who drank milk. The inclusion of a product term accounting for the interaction in the regression model resulted statistically significant and was convergent with the hypothesis of a joint beneficial effect for the concurrent exposure to the regular intake of milk and tea.

Whether the higher exposure to tobacco and alcohol of deprived individuals can or cannot explain the higher burden of head and neck cancer in poorer socioeconomic strata is a relevant research question in cancer epidemiology. Conway et al. [96] performed a mediation analysis to explain how much these detrimental behaviors explained the effect of income and education on the risk of the disease. Authors pooled 31 studies performed worldwide in a meta-analysis approach, thus estimating the remaining effect of education and income, after adjusting for tobacco and alcohol consumption. Lower socioeconomic status remained statistically associated with the disease, which suggests that the higher risk of poorer population strata is not solely attributable to their higher exposure to tobacco and alcohol. Statistically assessing conceptual pathways that may explain the remaining contribution of socioeconomic status to the disease, such as dietary habits and HPV infection, is an indication for further research.

11.6 The Effectiveness of Health Services

The epidemiological analysis has powerful tools to assess the effectiveness of health services in preventing, diagnosing, and treating tumors in the oral cavity and oropharynx. This section reviews some strategies used by epidemiological studies when it comes to instructing the planning of health services aimed at the disease.

Some studies tried to investigate the dissemination of knowledge on the disease in the population, mainly focusing when and how to access health units, in case of suspected oral cancer or persistent oral mucosal lesions. Obtaining the diagnosis and access to treatment for oral cancer depend on a complex interplay between several actors, such as the patient itself and health professionals at primary care and referral units.

How long do individuals and health practitioners take to act in the face of a suspect of the disease? What factors may anticipate or postpone the demand for healthcare? In Brazil, a study concluded that dentists, mainly those working in the public sector, were able to recognize the urgency associated with a suspected oral cancer case [97]. A systematic review [98] including 22 studies worldwide, many of them from high-income countries, concluded that the average interval from the first symptom to the start of treatment was 186.7 days, the more substantial part of it (80.3 days) being the patient delay in obtaining primary care.

The perception that early detection could reduce this interval fueled the proposition of screening strategies as

a promising perspective for oral cancer. However, a systematic review conducted in 2006 concluded that evidence to support or refute the recommendation of oral cancer screening by visual examination in the overall population is insufficient [99]. Subsequently, another systematic review reached to an analogous conclusion, observing no significant differences in mortality from oral cancer between screened and non-screened populations [100]. Nonetheless, the authors reported initial evidence (reduced to few studies and with high risk of bias) that the visual screening might be favorable among high-risk individuals, i.e., those who use tobacco, alcohol, or both. They also observed that the studies retrieved had not concluded the occurrence of physical or psychological harms associated with the visual screening of oral mucosa.

Several systematic reviews assessed the effectiveness of different treatment modalities. Chemotherapy, as an adjunct to radiotherapy and surgery, resulted in improved overall survival in oral cancer patients; its potential impact on survival might be even higher in cases of unresectable tumors [101]. Including 30 clinical trials, another systematic review [102] assessed which radiotherapy regimens resulted in better treatment outcomes for oral cancer. Authors concluded that fractionation radiotherapy resulted in improved overall survival, although the assessment of the clinical performance of radiotherapy would demand more accurate methods for reporting adverse events. As regards the evaluation of neck dissection surgery in patients with oral cancer, a review [103] reported weak evidence that elective neck dissection concurrently with the removal of the primary tumor results in advantages (reduced recurrence), when compared to the therapeutic procedure. However, evidence was insufficient to conclude on increases in survival. Authors recommended that future studies about treatment outcomes should assess health-related quality of life of patients.

Conclusion

Decades ago, Morris [104] synthesized the uses of epidemiology: monitoring the burden of disease over time and across space; evaluating health services; assessing prognosis, survival, and quality of life of patients; and analyzing the complex etiological chain of disease, the search for causes. The epidemiologic study of oral cancer is complex and involves multiple aspects. This chapter tried to follow Morris's lead by analytically exploring each of the themes he suggested.

This chapter described concepts and methods on how to assess the distribution of oral cancer in the population, its forms of measurement, and the principal associated factors. We reviewed methodological resources measuring the disease burden, in particular, the definition, estimation, and adjustment of incidence and death rates. Quantitative parameters provided here also included the assessment of patient survival and quality of life.

As refers to the appraisal of etiological and associated factors, this chapter summarized an intense effort of researchers worldwide in search of new clues and opportunities for prevention and improved prognosis. The distribution of oral cancer varies widely between the sexes and age groups; tobacco smoking and alcohol drinking are the main risk factors. Previous knowledge must be taken into consideration when formulating and appraising new hypotheses. The assessment of additional covariates, possibly exerting a subtler effect, has to observe multivariable schemes and adjustment for the complex etiological chain of the disease.

Epidemiology is of foremost relevance to the planning of health services and programs. Epidemiology must intervene when it comes to formulating initiatives in health education, programming services for diagnosis, treatment, and rehabilitation of patients, and assessing the effects of the disease on the population. Epidemiology provides conceptual frameworks to explain the distribution of the disease; epidemiology also provides methods and empiric data to appraise the effectiveness of health services, the access to early diagnosis, provision of high-quality treatments, and resources for patient rehabilitation.

To circumscribe, a theme with such a wide scope demands keeping updated an extensive review of references. The continuous monitoring of the literature allows bringing together distinct aspects of interest for the epidemiologic approach. We hope that the present effort of synthesis can be useful for students and researchers. We also hope that it may motivate new studies on this topic.

By describing and discussing these subjects, we tried to instigate the intelligence of the readers, encouraging their curiosity about new questions in this area. There are population groups to be studied, patients to be monitored, and knowledge gaps to be filled. A large branch of relevant literature awaits students and researchers planning to conduct their own epidemiological assessments about the disease. Hopefully, knowledge generated by these new studies will be useful for guiding health decision-making, health promotion, and social justice.

Points of Emphasis

The distribution of oral cancer varies widely between the sexes and age groups; tobacco smoking and alcohol drinking are the main risk factors. Previous knowledge must be taken into consideration when formulating and appraising new hypotheses. The assessment of additional covariates, possibly exerting a subtler effect, has to observe multivariable schemes and adjustment for the complex etiological chain of the disease. Epidemiology is of foremost relevance to the planning of health services and programs aimed at oral cancer. By describing and discussing these subjects, we tried to instigate the intelligence of the readers, encouraging them to perform their own studies on this subject. Hopefully, knowledge generated by these studies will allow guiding decision-making in the promotion of health and social justice.

References

1. Mahboubi E, Sayed GM. Oral cavity and pharynx. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. 2nd ed. New York: Oxford University Press; 1996. p. 583–95.
2. Moore SR, Pierce AM, Wilson DF. "Oral cancer" – the terminology dilemma. Oral Dis. 2000;6(3):191–3.
3. Tapia JL, Goldberg LJ. The challenges of defining oral cancer: analysis of an ontological approach. Head Neck Pathol. 2011;5(4):376–84.
4. Conway DI, Purkayastha M, Chestnutt IG. The changing epidemiology of oral cancer: definitions, trends, and risk factors. Br Dent J. 2018;225(9):867–73.
5. Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in human papillomavirus-associated cancers – United States, 1999-2015. MMWR Morb Mortal Wkly Rep. 2018;67(33):918–24.
6. Oosthuizen JC, Doody J. De-intensified treatment in human papillomavirus-positive oropharyngeal cancer. Lancet. 2019;393(10166):5–7.
7. Fritz A, Percy C, Jack A, Shanmugaratnam K, et al., editors. International classification of diseases for oncology (ICD-O), third edition (first revision). Geneva: World Health Organization; 2013.
8. Pindborg JJ. Epidemiological studies of oral cancer. Int Dent J. 1977;27(2):172–8.
9. Smith CJ, Pindborg JJ. Binnie WH, eds: Oral cancer; epidemiology, etiology, and pathology. New York: Hemisphere; 1990.
10. Kleinman DV, Swango PA, Pindborg JJ, Gupta PC. Toward assessing trends in oral mucosal lesions: lessons learned from oral cancer. Adv Dent Res. 1993;7(1):32–41.
11. Swango PA. Cancers of the oral cavity and pharynx in the United States: an epidemiologic overview. J Public Health Dent. 1996;56(6):309–18.
12. O'Hanlon S, Forster DP, Lowry RJ. Oral cancer in the North-East of England: incidence, mortality trends and the link with material deprivation. Community Dent Oral Epidemiol. 1997;25(5):371–6.
13. Moore S, Johnson N, Pierce A, Wilson D. The epidemiology of lip cancer: a review of global incidence and aetiology. Oral Dis. 1999;5(3):185–95.
14. Antunes JLF, Biazevic MGH, Araujo ME, Tomita NE, Chinellato LEM, Narvai PC. Trends and spatial distribution of oral cancer mortality in São Paulo, Brazil, 1980-1998. Oral Oncol. 2001;37(4):345–50.
15. Toporcov TN, Antunes JLF, Tavares MR. Fat food habitual intake and risk of oral cancer. Oral Oncol. 2004;40(9):925–31.
16. Komolmalai N, Chuachamsai S, Tantiwipawin S, et al. Ten-year analysis of oral cancer focusing on young people in northern Thailand. J Oral Sci. 2015;57(4):327–34.
17. Ong TK, Murphy C, Smith AB, Kanatas AN, Mitchell DA. Survival after surgery for oral cancer: a 30-year experience. Br J Oral Maxillofac Surg. 2017;55(9):911–6.
18. ThekkePurakkal AS, Naimi AI, Madathil SA, et al. Differential impact of socioeconomic position across life on oral cancer risk in Kerala, India: an investigation of life-course models under a time-varying framework. Community Dent Oral Epidemiol. 2018;46(6):592–600.
19. Monteiro LS, Antunes L, Santos LL, Bento MJ, Warnakulasuriya S. Survival probabilities and trends for lip, oral cavity and oropharynx cancers in Northern Portugal in the period 2000-2009. Ecancermedicalscience. 2018;12:855.
20. Choi E, Lee S, Nhung BC, et al. Cancer mortality-to-incidence ratio as an indicator of cancer management outcomes in Organization for Economic Cooperation and Development countries. Epidemiol Health. 2017;39:e2017006.
21. Forman D, Bray F, Brewster DH, et al., editors. Cancer incidence in five continents, IARC scientific publication no. 164, vol. X. International Agency for Research on Cancer: Lyon; 2014.
22. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância. Estimativa 2012: Incidência de câncer no Brasil. Rio de Janeiro: Ministério da Saúde, INCA; 2011.
23. Doll R, Cook P. Summarizing indices for comparison of cancer incidence data. Int J Cancer. 1967;2(3):269–79.
24. Lu TH, Shau WY, Shih TP, Lee MC, Chou MC, Lin CK. Factors associated with errors in death certificate completion. A national study in Taiwan. J Clin Epidemiol. 2001;54(3):232–8.
25. Murray CJL, Lopez AD. Measuring global health: motivation and evolution of the global burden of disease study. Lancet. 2017;390(10100):1460–4.
26. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
27. Pisani P, Bray F, Parkin DM. Estimates of the worldwide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002;97(1):72–81.
28. Doll R, Payne P. Waterhouse J (Eds.). Cancer incidence in five continents. I. a technical report. Berlin: Springer-Verlag; 1966.
29. Segi M, Fujisaku S, Kurihara M, Narai Y, Sasajima K. The age-adjusted death rates for malignant neoplasms in some selected sites in 23 countries in 1954-1955 and their geographical correlation. Tohoku J Exp Med. 1960;72:91–103.
30. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. Genebra: World Health Organization; 2004.. (GPE Discussion Paper Series: N.31 EIP/GPE/EBD)
31. Thompson LDR. Head and neck cancers. In: Stewart BW, Wild CP, editors. World cancer report. Lyon: International Agency for Research on Cancer; Geneva: World Health Organization; 2014. p. 422–31.
32. Stanford-Moore G, Bradshaw PT, Weissler MC, et al. Interaction between known risk factors for head and neck cancer and socioeconomic status: the Carolina Head and Neck Cancer Study. Cancer Causes Control. 2018;29(9):863–73.

33. Faggiano F, Partanen T, Kogevinas M, Boffetta P. Poverty and cancer. In: Kogevinas M, Pearce N, Susser M, Boffetta P, editors. Social inequalities and cancer. Lyon: IARC; 1997. [IARC Scientific Publications n. 138].
34. Maruthappu M, Watkins J, Noor AM, et al. Economic downturns, universal health coverage, and cancer mortality in high-income and middle-income countries, 1990-2010: a longitudinal analysis. Lancet. 2016;388(10045):684–95.
35. Teng AM, Atkinson J, Disney G, Wilson N, Blakely T. Changing socioeconomic inequalities in cancer incidence and mortality: cohort study with 54 million person-years follow-up 1981-2011. Int J Cancer. 2017;140(6):1306–16.
36. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459–544.
37. Shield KD, Ferlay J, Jemal A, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin. 2017;67(1):51–64.
38. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013;31(36):4550–9.
39. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer. 1994;73(1):187–90.
40. Gupta P, Migliacci JC, Hay A, et al. Validation and assessment of discordance of the 8th edition AJCC (American Joint Committee on Cancer) clinical and pathologic staging systems in patients with p16+ oropharyngeal cancer treated with surgery and adjuvant radiation at a single institution. Oral Oncol. 2018;83:140–6.
41. Carvalho AL, Ikeda MK, Magrin J, Kowalski LP. Trends of oral and oropharyngeal cancer survival over five decades in 3267 patients treated in a single institution. Oral Oncol. 2004;40(1):71–6.
42. Mupparapu M, Shanti RM. Evaluation and staging of oral cancer. Dent Clin N Am. 2018;62(1):47–58.
43. Gandara-Vila P, Perez-Sayans M, Suarez-Penaranda JM, et al. Survival study of leukoplakia malignant transformation in a region of northern Spain. Med Oral Patol Oral Cir Bucal. 2018;23(4):e413–20.
44. WHOQOL Group. Development of the WHOQOL: rationale and current status. Int J Ment Health 1994;23(Special issue: Quality of life assessment: cross-cultural issues – 2):24–56.
45. The WHOQOL Group. The World Health Organization quality of life assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998;46(12):1569–85.
46. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA Jr. The addition of mood and anxiety domains to the University of Washington quality of life scale. Head Neck. 2002;24(6):521–9.
47. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck module (QLQ-H&N35). Arch Otolaryngol Head Neck Surg. 2000;126(4):459–67.
48. Melissant HC, Jansen F, Schutte LER, et al. The course of sexual interest and enjoyment in head and neck cancer patients treated with primary (chemo)radiotherapy. Oral Oncol. 2018;83:120–6.
49. Biazevic MGH, Antunes JLF, Togni J, Andrade FP, Carvalho MB, Wünsch-Filho V. Immediate impact of primary surgery on health-related quality of life of hospitalized patients with oral and oropharyngeal cancer. J Oral Maxillofac Surg. 2008;66(7):1343–50.
50. Biazevic MGH, Antunes JLF, Togni J, Andrade FP, Carvalho MB, Wünsch-Filho V. Survival and quality of life of patients with oral and oropharyngeal cancer at 1-year follow-up tumor resection. J Appl Oral Sci. 2010;18(3):279–84.
51. Vartanian JG, Carvalho AL, Yueh B, et al. Brazilian-Portuguese validation of the University of Washington Quality of Life Questionnaire for patients with head and neck cancer. Head Neck. 2006;28:1115–21.
52. Hashibe M, Brennan P, Chuang S, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomark Prev. 2009;18(2):541–50.
53. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007;99(10):777–89.
54. Winn DM, Lee YC, Hashibe M, Boffetta P, INHANCE Consortium. The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer. Oral Dis. 2015;21(6):685–93.
55. Chuang SC, Jenab M, Heck JE, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control. 2012;23(1):69–88.
56. World Cancer Research Fund. American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington: WCRF/AICR; 007.
57. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustion Volume 100E – A review of human carcinogens. International Agency for Research on Cancer: Lyon; 2012.
58. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Cancer epidemiology and prevention. 4th ed. New York: Oxford University Press; 2017.
59. Kmietowicz Z. Data show "alarming" rise in oral cancers among people in their 40s. BMJ. 2009;339:b3293.
60. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: contemporary knowledge and future research considerations. Drug Alcohol Depend. 2015;156:1–13.
61. Conway D. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122(12):2811–9.
62. Tomatis L. Poverty and cancer. In: Kogevinas M, Pearce N, Susser M, Boffetta P, editors. Social inequalities and cancer. Lyon: IARC; 1997. [IARC Scientific Publications n.138].
63. Puigpinós R, Borrell C, Antunes JLF, et al. Trends in socioeconomic inequalities in cancer mortality in Barcelona: 1992-2003. BMC Public Health. 2009;9:35.
64. Antunes JLF, Toporcov TN, Biazevic MG, Boing AF, Bastos JL. Gender and racial inequalities in trends of oral cancer mortality in Sao Paulo, Brazil. Rev Saude Publica. 2013;47(3):470–8.
65. Lee CC, Chien SH, Hung SK, Yang WZ, Su YC. Effect of individual and neighborhood socioeconomic status on oral cancer survival. Oral Oncol. 2012;48(3):253–61.
66. Hirayama T. Nutritional intervention as a means of cancer prevention. In: Khogali M, Omar YT, Gjorgov A, Ismail AS, editors. Cancer prevention in developing countries. Proceedings of the 2nd UICC Conference on Cancer Prevention. Oxford: Pergamon Press; 1986. p. 287–9.
67. Galeone C, Turati F, Zhang ZF, et al. Relation of allium vegetables intake with head and neck cancers: evidence from the INHANCE consortium. Mol Nutr Food Res. 2015;59(9):1641–50.

68. Kawakita D, Lee YA, Turati F, et al. Dietary fiber intake and head and neck cancer risk: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. Int J Cancer. 2017;141(9):1811–21.
69. Galeone C, Edefonti V, Parpinel M, et al. Folate intake and the risk of oral cavity and pharyngeal cancer: a pooled analysis within the International Head and Neck Cancer Epidemiology Consortium. Int J Cancer. 2015;136(4):904–14.
70. Toporcov TN, Tavares GE, Rotundo LDB, et al. Do tobacco and alcohol modify protective effects of diet on oral carcinogenesis? Nutr Cancer. 2012;64(8):1182–9.
71. Biazevic MGH, Toporcov TN, Antunes JLF, et al. Cumulative coffee consumption and reduced risk of oral and oropharyngeal cancer. Nutr Cancer. 2011;63(3):350–6.
72. Miranda J, Monteiro L, Albuquerque R, et al. Coffee is protective against oral and pharyngeal cancer: a systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2017;22(5):e554–61.
73. Wang W, Yang Y, Zhang W, Wu W. Association of tea consumption and the risk of oral cancer: a meta-analysis. Oral Oncol. 2014;50(4):276–81.
74. Dasanayake AP, Silverman AJ, Warnakulasuriya S. Maté drinking and oral and oropharyngeal cancer: a systematic review and meta-analysis. Oral Oncol. 2010;46(2):82–6.
75. Boing AF, Antunes JLF, Carvalho MB, et al. How much do smoking and alcohol consumption explain socioeconomic inequalities in head and neck cancer risk? J Epidemiol Community Health. 2011;65(8):709–14.
76. Hakansson N, Floderus B, Gustavsson P, Feychting M, Hallin N. Occupational sunlight exposure and cancer incidence among Swedish construction workers. Epidemiology. 2001;12(5):552–7.
77. Siemiatycki J. Risk factors for cancer in the workplace. Boca Raton: CRC Press; 1991.
78. Richiardi L, Corbin M, Marron M, et al. Occupation and risk of upper aerodigestive tract cancer: the ARCAGE study. Int J Cancer. 2012;130(10):2397–406.
79. Velly AM, Franco EL, Schlecht N, et al. Relationship between dental factors and risk of upper aerodigestive tract cancer. Oral Oncol. 1998;34(4):284–91.
80. Sato F, Oze I, Kawakita D, et al. Inverse association between toothbrushing and upper aerodigestive tract cancer risk in a Japanese population. Head Neck. 2011;33(11):1628–37.
81. Hooper SJ, Wilson MJ, Crean SJ. Exploring the link between microorganisms and oral cancer: a systematic review of the literature. Head Neck. 2009;31(9):1228–39.
82. Tezal M, Grossi SG, Genco RJ. Is periodontitis associated with oral neoplasms? J Periodontol. 2005;76(3):406–10.
83. Yao QW, Zhou DS, Peng HJ, Ji P, Liu DS. Association of periodontal disease with oral cancer: a meta-analysis. Tumour Biol. 2014;35(7):7073–7.
84. Michaud DS, Fu Z, Shi J, Chung M. Periodontal disease, tooth loss, and cancer risk. Epidemiol Rev. 2017;39(1):49–58.
85. Guha N, Boffetta P, Wünsch Filho V, et al. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. Am J Epidemiol. 2007;166(10):1159–73.
86. Osso D, Kanani N. Antiseptic mouth rinses: an update on comparative effectiveness, risks and recommendations. J Dent Hyg. 2013;87(1):10–8.
87. Ahrens W, Pohlabeln H, Foraita R, et al. Oral health, dental care and mouthwash associated with upper aerodigestive tract cancer risk in Europe: the ARCAGE study. Oral Oncol. 2014;50(6):616–25.
88. Vaccarezza GF, Antunes JLF, Michaluart-Júnior P. Recurrent sores by ill-fitting dentures and intra-oral squamous cell carcinoma in smokers. J Public Health Dent. 2010;70(1):52–7.
89. Bouvard V, Baan R, Straif K, et al. WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens – part B: biological agents. Lancet Oncol. 2009;10(4):321–2.
90. Anantharaman D, Abedi-Ardekani B, Beachler DC, et al. Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. Int J Cancer. 2017;140(9):1968–75.
91. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010;39(1):166–81.
92. Brouwer AF, Eisenberg MC, Meza R. Age effects and temporal trends in HPV-related and HPV-unrelated oral cancer in the United States: a multistage carcinogenesis modeling analysis. PLoS One. 2016;11(3):e0151098.
93. VanderWeele TJ. Explanation in causal inference: developments in mediation and interaction. Int J Epidemiol. 2016;45(6):1904–8.
94. Antunes JLF, Toporcov TN, Biazevic MG, Boing AF, Scully C, Petti S. Joint and independent effects of alcohol drinking and tobacco smoking on oral cancer: a large case-control study. PLoS One. 2013;8(7):e68132.
95. Chen F, Yan L, Lin L, et al. Independent and joint effects of tea and milk consumption on oral cancer among non-smokers and non-drinkers: a case-control study in China. Oncotarget. 2017;8(30):50091–7.
96. Conway DI, Brenner DR, McMahon AD, et al. Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. Int J Cancer. 2015;136(5):1125–39.
97. Souza LM, Michel-Crosato E, Biazevic MGH, Antunes JLF. Scheduling delay in suspected cases of oral cancer. Rev Bras Epidemiol. 2011;14(4):642–50.
98. Varela-Centelles P, Seoane J, Lopez-Cedrun JL, et al. The length of patient and primary care time interval in the pathways to treatment in symptomatic oral cancer. A quantitative systematic review. Clin Otolaryngol. 2018;43(1):164–71.
99. Kujan O, Glenny AM, Oliver RJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev. 2006;3:CD004150.
100. Brocklehurst P, Kujan O, O'Malley LA, Ogden G, Shepherd S, Glenny AM. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev. 2013;11:CD004150.
101. Furness S, Glenny AM, Worthington HV, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. Cochrane Database Syst Rev. 2011;9:CD006386.
102. Glenny AM, Furness S, Worthington HV, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. Cochrane Database Syst Rev. 2010;12:CD006387.
103. Bulsara VM, Worthington HV, Glenny AM, et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database Syst Rev. 2018;12:CD006205.
104. Morris JN. Uses of epidemiology. BMJ 1955;2(4936):395–401. Int J Epidemiol. 2007;36(6):1165–72.

Dental Erosion

Karen Glazer Peres and Fabiana Vargas-Ferreira

Contents

12.1 Introduction – 210

12.2 Factors Associated with Dental Erosion – 210

12.2.1 Behavioral Factors – 211

12.3 Differential Diagnosis – 213

12.4 Classification of Dental Erosion – Indices – 214

12.5 Epidemiology of Dental Erosion – 216

12.5.1 Final Considerations – 218

References – 219

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_12

12.1 Introduction

Dental erosion is a relatively common oral condition [1], which may affect children, adolescents, and adult populations. Importance has been given to this condition due to its impact on individuals' quality of life. Also, worldwide epidemiologic and demographic transitions observed in the last decades have demanded new investigations in the oral health field. Significant achievements such as the decline of dental caries, seen mainly in children and adolescents during the previous century, as well as the longevity of the general population, increase the longevity of teeth and, consequently, their exposure to physiological and pathological wear. Although some erosive processes can exist without any clinical symptom, others may lead to continuing hypersensitivity, acute pain, or even pulp necrosis of the affected teeth [2]. Over the past decades, there has been an increased focus on epidemiological studies addressing the prevalence of dental erosion and its associated factors. Also, new risk factors of growing concern have been identified. This chapter updates the information on the distribution of dental erosion in primary and permanent dentitions across the world, variation in its classifications, and also discusses the factors associated with this condition in the new century.

12

12.2 Factors Associated with Dental Erosion

Dental erosion presents the main characteristics of the progressive and irreversible loss of dental structure due to chemical elements, biological, and behavioral factors, without microorganism involvement [3]. The report of the European Federation of Conservative Dentistry (EFCD) delivered during the Consensus Conference in Bern, Switzerland, on the 29th and 30th of April 2015, states that dental erosion is a chemical–mechanical process resulting in a cumulative loss of hard dental tissue not caused by bacteria [4]. As a consequence, the erosive process may include severe sensitivity, susceptibility to further erosion, mechanical wear, changes in occlusion, exposure of dental pulp, and compromised aesthetics. Factors associated with the development of dental erosion may be modified by the level of acknowledgement of an individual's general health aspects, differences in susceptibility of hard dental tissues, saliva characteristics, and socioeconomic conditions [5, 6].

The literature has shown that a small loss of dental substance is part of the normal physiological process of aging. Tooth wear is often a combination of attrition, abrasion, and erosion, in different proportions. These three processes can be differentiated as follows: attrition is the physiological wearing of hard dental hard tissue caused by tooth-to-tooth contact, and abrasion is caused by an object-to-tooth contact, such as toothbrushing. The loss of hard dental tissue by tooth erosion involves acids and not bacteria [6]. Usually, it is a general concurrence of any of the three processes, and this could result in an increased loss of tooth surface (Fig. 12.1).

Knowledge of the interrelationship between multifactorial aspects involved in the dental erosion process is crucial and helps to explain the fact that individuals exposed to the same risk factors may have different symptoms of tooth erosion. Three distinct mechanisms related to the destruction of the hard dental tissues co-occur in the process of dental erosion. Firstly, individuals experience absence or loss of salivary organic substances that cover the teeth. Secondly, loss of minerals from the dental surface occurs due to the presence of a decalcifying agent and, finally, the destruction of the tooth surface happens because of a biochemical, biophysical, or mechanical action [7].

Studies on sites of erosive lesions report that the pattern of damage depends on the exposure and the type of demineralizing agent. Factors considered extrinsic, such as diet-related acids, and intrinsic, such as gastric dysfunctions, can determine the appearance of erosion lesions at different locations on the surface of a tooth [8].

Potential associated factors to dental erosion can be grouped into three categories [5]: behavioral, biological, and socioeconomic factors.

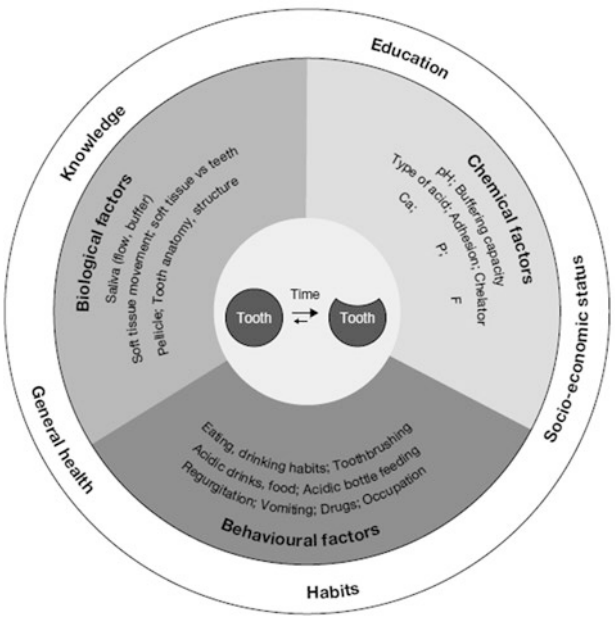


Fig. 12.1 Interactions of the different factors for the development of erosive tooth wear [5]

12.2.1 Behavioral Factors

Healthy diet and nutrition are essential for dental development and can affect different stages of this process, such as pre- and posteruptive periods. Dental caries, enamel hypoplasia, and dental erosion are examples of dental outcomes which may be associated with diet and nutritional aspects [9]. As healthy dietary habits also affect the general health positively by decreasing the occurrence of diseases such as obesity and cardiovascular illness, they are considered common risk and protective factors for both general and oral conditions [10]. The main factor associated with tooth erosion is the consumption of acidic drinks, mainly juices and soft drinks, by children and adolescents [11–17]. Some aspects have been suggested to influence the erosive potential of a drink, such as its pH and buffering capacity, the presence of adequate concentrations of calcium, fluoride, and phosphate, and the temperature of the drink [18–19]. Moreover, other aspects may be relevant, such as frequency of consumption [20], the time in contact with the acid [21], and unusual patterns of consumption [20]. High consumption of acidic fruits and food with other acidic components also contributes to the occurrence of tooth erosion, mainly, in older people [22].

Children and adolescents were the target population of a systematic review of the association between diet and dental erosion [23]. A search for original articles was conducted in different databases until May 2014, including observational studies, with subjects aged between 8 and 19 years of age. A total of 13 studies involving 16,661 children and adolescents showed an overall dental erosion prevalence of 34.1% (n = 5682). Sample sizes ranged from 605 to 3812 individuals. Studies comprised subjects living in higher- and middle-income countries, mainly from the United Kingdom (23.1%), Brazil (15.4%), and the Netherlands (7.7%). Dietary habits were obtained from brief dietary assessments (69.2%), and only 15.4% were assessed from the quantity of food – weighed or estimated. Findings indicated that consumption of carbonated drinks, natural acidic fruit juices, and confectionery and snacks were associated with a higher risk of dental erosion. High consumption of milk and yogurt significantly reduced the risk of having dental erosion. These findings are consistent with other investigations on diet and dental erosion. In a longitudinal study in the United Kingdom, children were examined at ages 12 and 14 years. Children with any consumption of carbonated drinks had nearly 60% and over twice a higher chance of having erosion at ages 12 and 14 years, respectively, than their counterparts. Those who consumed four or more glasses a day of this type of drink had 2.5- and a five times higher chance of having dental erosion at ages 12 and 14, respectively. In a longitudinal perspective, the consumption of carbonated drinks at age 12 resulted in a higher chance of developing erosion at age 14 [24]. Studies have suggested that the intake of sweet carbonated drinks is one of the most significant factors in the development of dental erosion [13]. Sweet carbonated drinks contain phosphoric acid and citric acid, and their pH is usually less than 4.0 [25]. Moreover, these beverages not only have a high content of sugar but also have high titratable acidity, which could be enough to induce tooth demineralization [24–25].

In the literature [17, 26–27], the consumption of milk and yogurt has been shown as having a protective effect against dental erosion. The large quantity of calcium and phosphate present in their composition may help control the demineralization process [17, 28]. Most of the available studies did not include possible confounder factors in the association between carbonated drinks' consumption and dental erosion, such as differences in salivary flow rate, buffering capacity, the number of consumed drinks, and specific patterns of drinking [8, 19, 27–28]. Also, no standard questionnaire for epidemiological surveys is available, which makes the comparison between studies difficult [29].

Measurement of diet is complex and represents significant challenges, especially in large populations and specific populations such as children and adolescents; also, its measurement is an essential component of much health-related research [30]. Lack of standard methodological aspects during data collection could also influence the assessment of diets, such as the extension, the period, the number of times required to record dietary habits [31], and even the day of the week when the measurement is collected [30]. Different patterns of drinking, such as swishing the drink around the mouth before swallowing or the use of a straw when consuming carbonated drinks, could influence the development of dental erosion [32–35]. Authors [36] have assessed the influence of six different patterns of drinking, and a lower pH was found when the drink was retained in the mouth. Another aspect which may influence the acidity of diet is the temperature of the drink. An in vitro study assessed four different types of drinking (yogurt, fermented milk, chocolate-based products, and fermented dairy beverages). Findings showed that at iced temperatures, all dairy beverages, except for the chocolate-based type, had a pH below the critical level for enamel and present potential corrosive properties [37]. However, another study showed that the external temperature is more prejudicial to the teeth than the iced one [38]. Findings on the influence of the temperature of drinks in the process of dental erosion are controversial and, therefore, not conclusive [19].

Children with dental caries have more chance to develop dental erosion [24, 39–41]. The common risk factor for both conditions is diet. Dietary habits are an essential risk factor for dental caries [42] and are a primary source of acids, contributing to the development of dental erosion [43]. Many types of food and soft drinks are not only acidic but also contain a high percentage of sugar, leading to the simultaneous occurrence of dental erosion and caries [39, 44–45]. The process and site specificity are different for both conditions. In general, the surfaces more prone to erosion are not those where caries occurs [12]. Dental erosion is often located in plaque-free areas, in opposition to dental caries, which are likely to be found in plaque-accumulation sites [46]. Dental caries and dental erosion can occur independently. The association between them may not always be found and, in some cases, the rapid and destructive nature of caries may force the removal of the clinical evidence of erosion [46]. More studies are necessary to better investigate the association between dental caries and erosion, since findings from other studies do not support such an association [12, 29, 44–45].

Gastroesophageal Reflux Gastroesophageal reflux (GR) disorder is relatively common in the pediatric population and has been associated with the presence of dental erosion with prevalence ranging from 14% to 87% in 1- to 18-year-old individuals having this condition [47]. The relationship between dental erosion and GR has been reported in some studies [16, 48–49]. Patients (average age of 21 years) with eating disorders had an 8.5-times increased risk of having dental erosion when compared to gender- and age-matched controls. Patients with a more extensive history of eating disorders had dental erosive lesions more often, and those with episodes of vomiting frequently had a 5.5-times higher risk of dental erosion than those without such a condition [50]. Despite this, the relationship between them is not well established [51–53], and findings from different studies are controversial [29, 34, 48, 54]. In addition, a systematic review and meta-analysis on eating disorders and dental erosion showed that patients with eating disorders had more risk of dental erosion (OR = 12.4, 95%CI = 4.1–37.5) and those with risk behavior of eating disorder had more risk of dental erosion than patients without such risk behavior (OR = 11.6, 95%CI = 3.2–41.7) [55]. These findings highlight the importance of dentists monitoring their patients regularly, sometimes throughout their childhood and adolescence. Therefore, they may be the first health professionals to suspect eating disorders, due to their oral implications, and therefore contribute to the patient's early referral to specific treatment [50].

Biological Factors Saliva properties, such as its composition, pH, flow rate, and buffering capacity, may have an influence on dental erosion and may also have an impact on the association between dental erosion and dental caries [19, 32, 54]. A case-control study, which involved 278 fifteen-year-olds in Iceland showed that the same proportion (22%) of cases (dental erosion group) and the controls had the low salivary buffering capacity [56].

The susceptibility to dental erosion may be different when compared to primary and permanent teeth. The deciduous tooth enamel has a lower thickness and mineralization than the permanent tooth enamel, which can provide a faster progression of erosive wear due to acid exposure [33, 57–58].

Another biological factor is the presence of defects of the enamel, such as hypoplasia. Very few studies investigated whether the presence of hypoplasia is associated with dental erosion [29, 40]. In a study conducted in Brazilian schoolchildren (n = 944), the presence of hypoplasia increased the chance of dental erosion by twice as much [29]. It has been suggested that abnormal enamel development may be a risk factor for dental erosion. The authors hypothesize that the reduced or altered mineralization observed in enamel defects may lead to the acceleration of the erosive process in the sites affected by hypoplastic lesions [29].

Demographic Characteristics The influence of sociodemographic factors on dental erosion is not conclusive. Some studies have shown higher prevalence and severity of dental erosion in boys compared to girls [12, 14, 16–17, 24, 26, 56, 58–64], while a few other studies found that girls had a higher experience of dental erosion [65, 66]. The higher experience of tooth wear into the dentine observed among boys could be attributed to differences in the strength of musculature and biting forces [67] or, on the other hand, it might be related to food preferences and behavioral and lifestyle factors. Compared with girls, boys are more likely to prefer sour foods and beverages with lower pH levels [68] and to practice intense physical activities, which may decrease salivary flow [69]. It remains unclear whether the gender differences observed in the prevalence of dental erosion are a result of biological or behavioral risk factors. These findings suggest that gender-specific interventions in the prevention of dental erosion might be an appropriate preventive approach [16].

In general, older children and adolescents have a higher prevalence of dental erosion than younger ones since this is a cumulative condition [13, 26, 29, 69–70]. Longitudinal studies are essential to monitor the progress of a disease or process in a population; however, there are limited data about dental erosion in terms of

incidence/progress rate. The baseline of a longitudinal study with Dutch children ($n = 552$) who attended a dental clinic (mean age 12 years) showed 26.7% of the children having at least one first molar with dental erosion, and 1.4% with erosive signs in the upper incisors. After 3 years of follow-up, the incidence of erosion in the upper incisors was 22.2%, and in the first molars, it was 14.8%, suggesting the cumulative aspect of this condition [17]. When the risk factor for dental erosion is not eliminated in the initial stages, the occurrence and severity may increase over time [28–29, 61].

Socioeconomic Factors It is well accepted that socioeconomic characteristics have a strong impact on oral health, both at an individual and at a global level. Relating to dental erosion, the findings are yet inconclusive. Generally, children from the "high" socioeconomic status had a higher experience of dental erosion than children from a "middle" or "low" socioeconomic status [21, 61, 67, 71–73]. The literature has suggested that families with a high income have higher living standards and tend to adopt lifestyles with more healthy dietary habits (consumption of fruits, vegetables, and juices) [46]. However, some studies have found a significantly higher prevalence of dental erosion amongst children and adolescents from more deprived backgrounds [20, 24, 40, 59, 74–75].

Another variable used as a proxy for socioeconomic status is the type of school attended. A Brazilian study showed that children from private schools had more dental erosion when compared with those registered at public schools [61]. The difference in the prevalence of dental erosion might be due to dietary habits and lifestyle among socioeconomic strata in developing and developed countries [14, 61]. Few studies have investigated the influence of the maternal educational level, and its influence on dental erosion [29, 64, 70, 72], but the findings are contradictory. A cross-sectional study conducted with 605 Greek preschool children showed that a higher maternal educational level was associated with a lower prevalence of dental erosion. The authors have explained that children whose mothers have a low level of education may adopt unhealthy dietary habits, which also predisposes them to dental erosion, such as carbonated soft drinks and fast food consumption. It is arguable that similar dietary habits, either healthy or unhealthy, that include high consumption of acidic food may subject children from different socioeconomic backgrounds to similar levels of risk for dental erosion [72].

Table 12.1 shows some demineralizing agents associated with the etiology of dental erosion with their respective wear patterns found in laboratory and epidemiological studies.

Table 12.1 Pattern of dental erosion and etiological factors

Acid sources associated with dental erosion	Erosion pattern
Diet	
Fruits, fruit juices, acidic beverages (*diet* and normal), sport drinks, aromatized drinks for children, food that is conserved, pickled, or preserved with vinegar, vitamin C.	It depends on dietary habit. For example, "sucking" citrus fruits may cause erosive defects on the incisal and buccal surfaces of the upper incisors.
Products and medicines	
Acetylsalicylic acid (aspirin), replacement of hydrochloric acid and isotonic beverages (iron tonics), excessive use of high abrasive dentifrices, illicit drugs.	Loss of dental structure may occur on the occlusal surface of the lower molars and the occlusal and palatal surfaces of the upper molars. It may also happen on the buccal surfaces of the upper anterior and posterior teeth.
Diseases and general health conditions	
Hernia, recurrent vomiting due to pregnancy or alcoholism, diabetes mellitus, drugs that cause nausea, radiotherapy, anorexia nervosa, bulimia, other eating disorders, xerostomia	Loss of dental structure may be related to the occlusal surface of the molars and the palatal surface of the anterior and premolar teeth
OCCUPATION	
Workers who have regular contact with aerosols, sulfuric acid, hydrochloric acid, laboratory products, swimmers, and wine tasters	Most of these substances affect the buccal surface of the upper and lower anterior teeth
Ferreira & Pozzobon [37]	

12.3 Differential Diagnosis

Early diagnosis of erosion is considered difficult since the erosive process usually occurs associated with other types of dental wear. Also, the first erosive signs have few clinical onsets and no apparent symptoms; however, the area affected by wear and its clinical appearance may help to determine the predominant etiology. It is paramount to conceptualize that all types of tooth wear cause irreversible loss of the external surface of the tooth and, in some individuals, the presence of tooth wear may be multifactorial. For this reason, the differential diagnosis between the chemical and mechanical nature of erosion lesions is complicated.

The noncarious destructive processes of dental wear that should be taken into consideration in the differential diagnosis of dental erosion are abrasion, attrition, and abfraction. Dental abrasion is the pathological wear of hard dental tissue caused by abnormal mechanical processes, such as the use of objects or substances repeatedly introduced into the mouth and that come in contact with the teeth. It does not include the bruises caused by chewing or those resulting from the contact between the teeth. Abrasive surfaces are characterized by defects in the mineralized surface of the teeth and have a polished appearance. Abrasive lesions are usually more severe on one side of the mouth than on the other because of the different force exerted in toothbrushing. It may also be associated with gingival recession [76]. Dental attrition is the pathological wear of hard dental tissue because of contact between teeth (grinding), without the presence of any foreign substance causing interference. Such contact involves the occlusal and incisal surfaces of the teeth. The lesion is directly and positively associated with age, clinically presenting the formation of facets. The dental surface with an attrition process has an extremely polished and smooth appearance with multiple facets [9, 76]. Abfraction is a particular form of contour defect of the cement-enamel junction, and refers to lesions observed in a single tooth, resulting from eccentric occlusal forces that lead to dental flexion, causing microfractures that propagate perpendicularly from the long axis of the tooth [76].

The characteristics considered as pathognomonic of erosive wear are the absence of the macroscopic plate, excessive brightness, and surrounded by an apparent translucent halo. In the posterior teeth, the progression of occlusal erosion leads to a rounding of the cusps and restorations rising above the level of the surfaces of adjacent teeth. In severe cases, occlusal morphology disappears, and extensive loss of enamel may lead to exposure of the dentin and even lead to pulpal exposure, making the teeth sensitive to hot and cold foods and tactile stimuli [46]. If the etiologic factor is not removed or controlled, the erosive lesion tends to progress and reach the dentin or even approach the pulp tissue [11–12]. Common sites for erosion in the deciduous dentition are the molar occlusal and the incisal or palatal surfaces of the anterior upper teeth. Cervical lesions rarely occur in children in the deciduous dentition [76].

12.4 Classification of Dental Erosion – Indices

In the field of epidemiology, there are minimum requirements for indices and indicators being considered as adequate. They should be easy to learn; be able to show good intra- and inter-examiner agreement; allow differentiation between various degrees of severity and between different types of defects, and be sensitive enough to monitor the progression of the lesions over time [48]. Numerous indices have been proposed to measure dental wear and, more specifically, dental erosion. All indices available to measure dental erosion have advantages and disadvantages, including a greater or lesser amount of information that can be collected. It is suggested that the existence of several indices may be related to the difficulty in identifying the erosive process based on only one cause, mainly because of the simultaneous presence of other types of wear [77].

There is a considerable variation in dental erosion indices, the majority of which were developed from the late nineteenth century to the early twenty-first century. They differ on the number of recorded teeth, type of recording (clinical vs. based on photographs or models), choice of the reference value (individual, teeth or tooth side), calibration procedures, and determination of the outcome (yes/no decision, shape of the lesion, estimation of severity, and quantification of dimension of tissue loss). Therefore, comparisons between studies related to the frequency and distribution of erosion must be cautiously analyzed due to the lack of a gold-standard index. Studies have reported as the main problems concerning dental erosion indices the lack of sensitivity to accompanying changes in tooth surface loss, difficulty in defining the score when considering each dental element as a unit of analysis, and a lack of differentiation of dental tissues lesion, which does not allow an adequate evaluation of the severity of the lesions. Most of the existing indices measure tooth wear and may concurrently include lesions of erosion, abrasion, and attrition [77].

The analysis of dental erosion using indices should allow for the exclusion of teeth and conditions that prevent the careful evaluation of the dental surface, such as teeth with fractures, extensive restorations, the presence of orthodontic appliances, and enamel or dentin hypoplasia on the surface. In these cases, the teeth should not be included in the analysis. The choice of an index has an impact on the study outcome and might be one determinant of the dimension of erosion prevalence.

Studies that proposed analyzing tooth wear in humans have initially performed the clinical evaluation of the lesions by estimating their severity [78] and, later, by observing their distribution as well.

The Index proposed by Eccles [78] classifies dental erosion according to the severity of the lesions (Classes I, II, and III) and evaluates the location and extent of enamel and dentin surface area(s). This Index was also developed to measure dental wear in adults, where various wear conditions may overlap. Class III lesions may still be classified depending on the surface involved by erosion, as can be seen in Table 12.2.

Table 12.2 Eccles index [78] for dental erosion

Scores	Surface	Criteria
Class I		Early stages of erosion, absence of developmental ridges, smooth, glazed surface occurring mainly on labial surfaces of maxillary incisors and canines
Class II	Buccal	Dentine involved for less than one-third of the surface; two types Type 1 (commonest): ovoid–crescentic in the outline, concave in the cross section at the cervical region of the surface. Must differentiate from wedge-shaped abrasion lesions
Class IIIa	Buccal	More extensive destruction of dentine, affecting anterior teeth particularly. Majority of lesions affect a large part of the surface, but some are localized and hollowed out
Class IIIb	Lingual or palatal	Dentine eroded for more than one-third of the surface area. Gingival and proximal enamel margins have white, etched appearance. Incisal edges translucent due to loss of dentine. Dentine is smooth and anteriorly is flat or hollowed out, often extending into secondary dentine
Class IIIc	Incisal or occlusal	Surfaces involved in the dentine appearing flattened or with cupping. Incisal edges appear translucent due to undermined enamel; restorations are raised above the surrounding tooth surface
Class IIId	All	Severely affected teeth, where both labial and lingual surfaces are extensively involved. Proximal surfaces may be affected; teeth are shortened

Table 12.3 Tooth wear index (TWI) [79]

Scores	Surface	Criteria
0	Buccal/lingual/ occlusal/incisal	No loss of enamel surface characteristics
	Contour	No loss of contour
1	Buccal/lingual/ occlusal/incisal	Loss of enamel surface characteristics
	Contour	Minimal loss of contour
2	Buccal/lingual/ occlusal	Loss of enamel exposing dentine for less than one-third of the surface
	Incisal	Loss of enamel just exposing the dentine
	Contour	Defect less than 1 mm deep
3	Buccal/lingual/ occlusal	Loss of enamel exposing the dentine for more than one-third of the surface
	Incisal	Loss of enamel and substantial loss of dentine
	Contour	Defect less than 1–2 mm deep
4	Buccal/lingual/ occlusal	Complete enamel loss–pulp exposure–secondary dentine exposure
	Incisal	Pulp exposure or exposure of secondary dentine
	Contour	Defect more than 2 mm deep–pulp exposure–secondary dentine exposure

Smith and Knight [79] proposed the most widely used index for assessing tooth wear (erosion, abrasion, and attrition) in 1984. The TWI (Tooth Wear Index) does not presuppose the etiology but is widely used in epidemiological research. This index evaluates the buccal, lingual or palatal, occlusal and incisal surfaces; it proposes scores ranging from 0 to 4, establishes criteria that only involve the enamel, enamel/dentin and enamel/dentin/pulp involved in different degrees. The Eccles Index, TWI index, was developed to measure dental wear in adults, where the overlapping of various types of wear may exist. As this index is not specific for erosion assessment, its use may overestimate any evaluated condition. The criteria assessed are shown in Table 12.3.

Another index worthy of some attention was developed by Lussi et al. [80] This index has been widely used in European studies to evaluate the site, dentine exposure, and the dimension of exposure on the buccal, lingual, and occlusal surfaces of all teeth, except for permanent third molars. The criteria are described in Table 12.4.

O'Brien [81] in an epidemiological study conducted in the United Kingdom in 1993 used an index to measure tooth erosion that assesses the depth of the lesions and the area of the dental surface involved. The buccal, lingual or palatal, occlusal and incisal surfaces are recorded with scores from 0 to 3. The criteria include only enamel, enamel/dentin, and enamel/dentin/pulp involved in different degrees, and it also adds information on the extent of the area involved by the lesion. When a tooth is not subject to examination for any reason, it receives a specific code. This index was developed for use in children with deciduous dentition, but it is also used to evaluate permanent teeth and primarily uses descriptive and qualitative aspects (Table 12.5).

Table 12.4 Erosion index according to Lussi [80]

Surface	Scores	Criteria
Buccal	0	No erosion. Surface with a smooth, silky glazed appearance, possible absence of developmental ridges
	1	Loss of surface enamel. Intact enamel cervical to the erosive lesion; concavity on enamel where breadth clearly exceeds depth, thus distinguishing it from toothbrush abrasion. Undulating borders of the lesion are possible and the dentine is not involved
	2	Involvement of dentine for less than half of the tooth surface
	3	Involvement of dentine for more than half of the tooth surface
Occlusal/ lingual	0	No erosion. Surface with a smooth, silky glazed appearance, possible absence of developmental ridges
	1	Slight erosion, rounded cusps, edges of restorations rising above the level of the adjacent surface
	2	Severe erosions, more pronounced signs than in Grade 1. Dentine is involved

Table 12.5 UK National Survey of Children's Dental Health index [81]

Scores	Criteria
Deepness	
0	Normal
1	Enamel only – on incisor teeth there is a loss of developmental ridges resulting in smooth, glazed, or "ground glass" appearance. On occlusal surfaces, the cusps appear rounded and there may be depressions producing "cupping"
2	Enamel and dentine – there is loss of enamel, exposing the dentine. On incisors, this may resemble a "shoulder preparation" parallel to the crest of the gingivae, particularly on the palatal surfaces. The incisors may appear shorter and there may be chipping of the incisal edges. On occlusal surfaces, "cupping" and rounding-off of cusps is evident. Restorations may be raised above the level of the adjacent tooth surface
3	Enamel, dentine, and pulp – loss of enamel and dentine resulting in pulpal exposure.
9	Assessment cannot be made
Area	
0	Normal
1	Less than 1/3 of the involved surface
2	1/3 to 2/3 of the involved surface
3	More than 2/3 of the involved surface
9	Assessment cannot be made

Given the necessity of a more detailed diagnosis of dental erosion in epidemiological research, O'Sullivan [82] proposed an index to measure different types of wear, especially dental erosion. This index was designed for use in children, for both deciduous and permanent dentition. It lists the affected dental surfaces, the severity of the erosion (different degrees), and the affected surface area. This index allows longitudinal follow-up studies with sensitive records of the alterations that have occurred concerning the degree of wear. It is possible to monitor the progression of the lesion and to evaluate the success of some preventive measures proposed to individuals who are affected by dental erosion (Table 12.6).

In 2008, a new index called Basic Erosive Wear Examination (BEWE) [83] was developed. This index recommends the sum of the highest scores of each sextant to determine the level of risk, which in turn corresponds to the clinical procedures indicated for the management of the case. For example, individuals whose cumulative score of all sextants achieve between 9 and 13 points, are classified as a medium risk. The procedures correspond to oral hygiene evaluation and diet; identification of the main etiological factors for the loss of dental tissue; and the development of strategies to eliminate the respective impacts; in addition to the use of fluoride to increase the resistance of dental surfaces and the orientation for a dental check-up every 6 months. As a disadvantage of BEWE, it is noted that when considering only the highest scores of each sextant, many data could be lost. The distribution and severity of erosive lesions per tooth are not adequately recorded when BEWE is applied. All the criteria are shown in Table 12.7.

12.5 Epidemiology of Dental Erosion

There is a growing concern that the prevalence of dental erosion is increasing, especially in children and adolescents. Data from epidemiological studies from different countries have shown a wide range of prevalence and/or incidence varying from 7.1% to 52.9%. Different indices and criteria applied to measure this condition may influ-

Table 12.6 Tooth erosion: O'Sullivan's index [82]

Site	Surface
A	Buccal only
B	Palatal or lingual only
C	Incisal or occlusal only
D	Buccal and incisal
E	Palatal and incisal/occlusal
F	Multisurface
	Severity
0	Normal enamel
1	Matt appearance of the enamel surface with no loss of contour
2	Loss of enamel only (loss of surface contour)
3	Loss of enamel with exposure of dentine (enamel–dentin junction visible)
4	Loss of enamel and dentine beyond the enamel–dentin junction
5	Loss of enamel and dentine with exposure of the pulp
9	Unable to assess (e.g., tooth crowned or large restoration)
	Surface area
	< 50%
	≥ 50%

Table 12.7 Basic Erosive Wear Examination (BEWE) [83]

Scores	Criteria
0	No erosive tooth wear
1	Initial loss of surface texture
2[a]	Distinct defect, hard tissue loss involving <50% of the surface area
3[a]	Hard tissue loss involving >50% of the surface area

[a]Scores 2 and 3, dentine is often involved

ence such variation as well as the variation in the investigated groups of age [24, 29].

A meta-analysis of studies (n = 3071 children) on the prevalence of tooth wear, including dental erosion in preschool children, highlights the importance of dental erosion as a crucial pathological entity such as dental caries in the primary dentition. Authors have found only three studies on tooth wear in deciduous teeth. The prevalence of dental erosion ranged from 5% to 35% and the main methodological difference between the studies was the tooth wear index used [84]. Also, the study showed that tooth wear involving the dentine of deciduous teeth increases linearly with age [84]. The authors suggest that children should be monitored in the initial stages of tooth wear, including dental erosion, to maintain the tooth surface and prevent the exposure of the dentine. Moreover, strategies to reduce the intake of soft drinks by children is a common risk-approach which may have multiple benefits preventing not only tooth wear in childhood and later life, but also many other general and oral health diseases [85].

When adults were the target population in studies of the prevalence of tooth wear, including dental erosion, a systematic review identified severe tooth wear varying from 3% at the age of 20 years to 17% at the age of 70 years. Increasing levels of tooth wear are significantly associated with age [86].

Children and adolescents were the target population in two systematic reviews [1, 87] which investigated the development of tooth wear. The first study included subjects (up to 18 years old) with primary, permanent, and mixed dentitions, and evaluated dental erosion, attrition, and abrasion. A search was carried out in PubMed and Medline from January 1980 to September 2008, using the following combinations of keywords "tooth wear," "attrition," "erosion," "abrasion," and "prevalence" and generated 2230 records. A total of 29 studies were included in the systematic review. Most studies were conducted in the United Kingdom and the remainder ranged across the continents. The ages ranged between 1.5 and 18 years. Fourteen studies included subjects younger than 7 years, which studied the deciduous dentition. Nine different tooth wear indices were used. The TWI original and its modifications were used in 24 studies. Prevalence of tooth wear involving dentine ranged from 0 to 82% in deciduous teeth and from 0 to 54% in permanent teeth of children 7 years and older. The systematic review indicated that the prevalence of tooth wear leading to dentine exposure in deciduous teeth increased with age [1].

Another systematic review [87] covered specifically the signals of dental erosion. A search for original articles was conducted in PubMed, Medline, ISI Web of Knowledge, Scopus, Scientific Electronic Library Online (SciELO), Latin American and Caribbean Health Sciences (LILACS) from early 2014 to March 2014. The search strategy included "dental erosion," "erosive tooth wear," "tooth erosion," and "child," "children," "adolescents," and other combinations and generated 1512 publications. A total of 22 population-based studies included in the meta-analysis showed an estimated combined prevalence of dental erosion in permanent teeth equal to 30.4% (95%CI 23.8–37.0). Only two analyzed studies had longitudinal [24, 62] sample sizes ranging from 200 [88] to 150,763 [63] individuals. Some studies

Table 12.8 Prevalence and/or incidence of dental erosion in children and adolescents (2015–2018)

Authors/year	Design	Country	Sample size	Index	Prevalence/incidence CI95%
Al Habin et al. [41] 2018	Cross-sectional	Malaysia	598	BEWE	45.0% (41.0–49.0)
Salas et al. [70] 2017	Cross-sectional	Brazil	1210	O'Sullivan	25.1% (22.7–27.7)
Brusius et al. [90] 2018	Longitudinal	Brazil	801	BEWE	7.1% (5.4–9.1)
Loureiro et al. [64] 2015	Cross-sectional	Uruguay	1136	BEWE	52.9% (49.9–55.8)
Muller-Bolla et al. [75] 2015	Cross-sectional	France	331	BEWE	39.0% (33.7–44.4)
Alves et al. [14] 2015	Cross-sectional	Brazil	1528	BEWE	15.0% (13.2–16.9)

comprised subjects living in low- and middle-income countries such as Brazil [23, 28–29, 61], Libya [44], and India [89], and others from high-income countries such as the United Kingdom [8, 12, 24] and the United States [26]. The main variables that showed an effect on the prevalence were clinical indices used for dental erosion, sample size, and geographic location. The TWI was associated with two-times higher prevalence rates of dental erosion when compared with the O'Sullivan index. As the TWI is not a specific index to detect dental erosion, this may have overestimated the obtained prevalence. Sample sizes greater than 1000 subjects presented different rates from those with less than 1000 individuals enrolled. Finally, the Middle East and Africa presented the highest prevalence ratio (41.4%), almost twice as great as the rates observed in America and Asia [87].

Studies on the prevalence of dental erosion published from 2015 are presented in Table 12.8. Most of the study designs were cross-sectional studies and involved children and adolescents from Brazil, France, Uruguay, and Malaysia. The sample size ranged from 331 to 1528 individuals. The index most used was BEWE. The prevalence ranged from 15.0% to 52.9%.

12.5.1 Final Considerations

Dental erosion is considered an expected oral health condition, and there is evidence that approximately one-third of children and adolescents have some level of dental erosion in permanent teeth [23]. It has been suggested that dental erosion has a multifactorial etiology. The interrelationship between chemical, biological, socioeconomic, and behavioral factors may explain the variation in dental erosion prevalence among different populations. Also, the use of different indices to measure dental erosion may affect differences in the magnitude of dental erosion prevalence between countries and populations. Dental erosion can lead to a range of consequences depending on the etiological factors involved and the severity of the erosion lesion. Teeth may present crown destruction, or, in severe cases, early tooth loss may occur. Erosion can also modify the development of masticatory and phonetic functions, and be associated with discomfort and pain [2], tooth sensitivity, enamel trauma, and aesthetic changes [40], despite in low levels of severity its does not negatively impact the quality of life of the affected individuals [91]. Early diagnosis facilitates the approach targeted toward the patient avoiding the exposure to factors associated with this condition. Due to the complex nature of the erosive process, a more comprehensive preventive approach is recommended to identify people at risk of developing such a condition. Monitoring erosion lesions and the implementation of educational and preventive measures are suggested for those at risk of developing dental erosion.

Point of Emphasis

- Dental erosion is a growing concern among clinicians and epidemiologists that presents multifactorial etiology;
- There is a wide range of different scoring systems to assess erosion, with a significant variation in sample sizes and participants' age in epidemiologic studies;
- Relevance: heterogeneous data on the prevalence of dental erosion is found worldwide;
- Prevalence of dental erosion increases with age, and there is a trend for a marked rate of erosion in younger age groups.

References

1. Kreulen CM, Van't Spijker A, Rodriguez JM, Bronkhorst EM, Creugers NH, Bartlett DW. Systematic review of the prevalence of tooth wear in children and adolescents. Caries Res. 2010;44(2):151–9.
2. Sivasithamparam K, Harbrow D, Vinczer E, Young WG. Endodontic sequelae of dental erosion. Aust Dent J. 2003;48(2):97–101.
3. Ten Cate JM, Imfeld T. Dental erosion, summary. Eur J Oral Sci. 1996;104(2PT2):242–4.
4. Shellis RP, Ganss C, Ren Y, Zero DT, Lussi A. Methodology and models in erosion research: discussion and conclusions. Caries Res. 2011;45(suppl 1):69–77.
5. Huysmans MC, Chew HP, Ellwood RP. Clinical studies of dental erosion and erosive wear. Caries Res. 2011;45(suppl 1):60–8.
6. Lussi A, Schaffner M. Progression of and risk factors for dental erosion and wedge-shaped defects over a 6-year period. Caries Res. 2000;34:182–7.
7. Zero DT. Etiology of dental erosion-extrinsic factors. Eur J Oral Sci. 1996;104(2):162–77.
8. Willians D, Croucher R, Marcenes W, O'Farrel M. The prevalence of dental erosion in the maxillary incisors of 14 year-old school-children in Tower Hamlets and Hackney, London, U.K. Int Dent J. 1999;49(4):211–6.
9. Lussi A, Jaeggi T, Zero D. The role of diet in the aetiology of dental erosion. Caries Res. 2004;38:34–44.
10. Sheiham A, Watt RG. The common risk factor approach: a rational basis for promoting oral health. Community Dent Oral Epidemiol. 2000;28(6):399–406.
11. Auad S, Moynihan P. Diet and dental erosion. Quintessence Int. 2007;38(2):130–3.
12. Bardolia P, Burnside G, Ashcroft A, Milosevic A, Goodfellow SA, Rolfe EA, et al. Prevalence and risk indicators for erosion in thirteen-to fourteen-years-olds on the Isle of Man. Caries Res. 2010;44(2):165–8.
13. González-Aragón AE, Borges-Yañez SA, Lussi A, Irigoyen-Camacho ME, Medina FA. Prevalence of erosive tooth wear and associated factors in a group of Mexican adolescents. J Am Dent Assoc. 2016;147(2):92–7.
14. Alves LS, Brusius CD, Damé-Teixeira N, Maltz M, Susin C. Dental erosion among 12-year-old schoolchildren: a population-based cross-sectional study in South Brazil. Int Dent J. 2015;65(6):322–30.
15. Hamasha AA, Zawaideh FI, Al-Hadithy RT. Risk indicators associated with dental erosion among Jordanian school children aged 12-14 years of age. Int J Paediatr Dent. 2014;24(1):56–68.
16. Mulic A, Skudutyte-Rysstad R, Tyeit AB, Skaare AB. Risk indicators for dental erosive wear among 18-yr-old subjects in Oslo, Norway. Eur J Oral Sci. 2012;120(6):531–8.
17. El Aidi H, Bronkhorst EM, Huysmans MC, Truin GJ. Multifactorial analysis of factors associated with the incidence and progression of erosive tooth wear. Caries Res. 2011;45(3):303–12.
18. Al-Dlaigan YH, Shaw L, Smith A. Dental erosion in a group of British 14-year-old school children. Part II: influence of dietary intake. Br Dent J. 2001;190(5):258–61.
19. Correr GM, Alonso RC, Correa MA, Campos EA, Baratto-Filho F, Puppin-Rontani RM. Influence of diet and salivary characteristics on the prevalence of dental erosion among 12-year-old schoolchildren. J Dent Child. 2009;76(3):6–12.
20. Wang P, Lin HC, Chen JH, Liang HY. The prevalence of dental erosion and associated risk factors in 12–13-year-old school children in Southern China. BMC Public Health. 2010;10:478.
21. Van Rijkom HM, Truin GJ, Frencken JE, König KG, van´t Hof MA, Bronkhorst EM, et al. Prevalence, distribution and background variables of smooth-bordered tooth wear in teenagers in the Hague, the Netherlands. Caries Res. 2002;36(2):147–54.
22. Jarvinen VK, Rytomaa II, Hinonen OP. Risk factors in dental erosion. J Dent Res. 1991;70(6):942–7.
23. Salas MM, Nascimento GG, Vargas-Ferreira F, Tarquinio SB, Huysmans MC, Demarco FF. Diet influenced tooth erosion prevalence in children and adolescents: results of a meta-analysis and meta-regression. J Dent. 2015;43(8):865–75.
24. Dugmore CR, Rock WP. A multifactorial analysis of factors associated with dental erosion. Br Dent J. 2004;196(5):283–6.
25. Lussi A, Megert B, Shellis RP, Wang X. Analysis of the erosive effect of different dietary substances and medications. Br J Nutr. 2012;107(2):252–62.
26. Okunseri C, Okunseri E, Gonzalez C, Visotchy A, Szabo A. Erosive tooth wear and consumption of beverages among children in the United States. Caries Res. 2011;45(2):130–5.
27. Çaglar E, Kargul B, Tanboga I, Lussi A. Dental erosion among children in an Istanbul public school. J Dent Child. 2005;72(1):5–9.
28. Gurgel CV, Rios D, Buzalaf MA, da Silva SM, Araújo JJ, Pauletto AR, et al. Dental erosion in a group of 12- and 16-year-old Brazilian schoolchildren. Pediatr Dent. 2011;33(1):23–8.
29. Vargas-Ferreira F, Praetzel JR, Ardenghi TM. Prevalence of tooth erosion and associated factors in 11-14-year-old Brazilian schoolchildren. J Public Health Dent. 2011;71(1):6–12.
30. Watson JF, Collins CE, Sibbritt DW, Dibley MJ, Garg ML. Reproducibility and comparative validity of a food frequency questionnaire for Australian children and adolescents. Int J Beh Nut Phys Act. 2009;6:62.
31. Thompson FE, Byers T. Dietary assessment resource manual. J Nut. 1994;124(suppl):22458–317S.
32. O'Sullivan EA, Curzon ME. A comparison of acidic dietary factors in children with and without dental erosion. ASDC J Dent Child. 2000;67(3):186–92.
33. Al-Majed M. A, Murray JJ. Prevalence and risk factors for dental erosion in 5-6-year-old and 12-14 year old boys in Saudi Arabia. Community Dent Oral Epidemiol. 2002;30(1):38–46.
34. Rios D, Magalhães AC, Honório HM, Buzalaf MA, Lauris JR, Machado MA. The prevalence of deciduous tooth wear in six-year-old children and its relationship with potential explanatory factors. Oral Health Prev Dent. 2007;5(3):167–71.
35. Hasselkvist A, Johansson A, Johansson AK. A 4-year prospective longitudinal study of progression of dental erosion associated to lifestyle in 13-14-year-old Swedish adolescents. J Dent. 2016;47:55–62.
36. Johansson AK, Lingstrom P, Imfeld T, Birkhed D. Influence of drinking method on tooth surface pH in relation to dental erosion. Eur J Oral Sci. 2004;112(6):484–9.
37. Ferreira FV, Pozzobon RT. Processed dairy beverages pH evaluation: consequences of temperature. J Clin Pediatr Dent. 2009;33(4):319–23.
38. Amaechi BT, Higham SM, Edgar WM. Factors influencing the development of dental erosion in vitro: enamel type, temperature, and exposure time. J Oral Rehabil. 1999;26(8):624–30.
39. Al-Malik MI, Holt RD, Bedi R. Erosion, caries and rampant caries in preschool children in Jeddah, Saudi Arabia. Community Dent Oral Epidemiol. 2002;30(1):16–23.
40. Kazoullis S, Seow WK, Holcombe T, Newman B, Ford D. Common dental conditions associated with dental erosion in schoolchildren in Australia. Pediatr Dent. 2007;29(1):33–9.
41. Ab Halim N, Esa R, Chew HP. General and erosive tooth wear of 16-year-old adolescents in Kuantan, Malaysia: prevalence and association with dental caries. BMC Oral Health. 2018;18(1):11.

42. Perera I, Ekanayake L. Relationship between dietary patterns and dental caries in Sri Lankan adolescents. Oral Health Prev Dent. 2010;8(2):165–72.
43. Auad SM, Waterhouse PJ, Nunn JH, Moynihan PJ. Dental caries and its association with sociodemographics, erosion, and diet in schoolchildren from Southeast Brazil. Pediatr Dent. 2009;31(3):229–35.
44. Huew R, Waterhouse P, Moynihan P, Kometa S, Maguire A. Dental caries and its association with diet and dental erosion in Libyan schoolchildren. Int J Paediatr Dent. 2012;22(1):68–76.
45. Salas MMS, Dantas RVF, Ramalho HS, Vargas-Ferreira F, Torriani D, Demarco FF. Tooth erosion and dental caries in schoolchildren: is there a relationship between them? Braz J Oral Sci. 2014;13(1):12–6.
46. Taji S, Seow WK. A literature review of dental erosion in children. Aust Dent J. 2010;55(4):358–67.
47. Marsicano JA, de Moura-Grec PG, Bonato RC, Sales-Peres Mde C, Sales-Peres A, Sales-Peres SH. Gastroesophageal reflux, dental erosion, and halitosis in epidemiological surveys: a systematic review. Eur J Gastroenterol Hepatol. 2013;25(2):135–41.
48. Jensdottir T, Arnadottir IB, Thorsdottir I, Bardow A, Gudmundsson K, Theodors A, et al. Relationship between dental erosion, soft drink consumption and gastroesophageal reflux among Icelanders. Clin Oral Invest. 2004;8(2):91–6.
49. Skalsky Jarkander M, Grindefjord M, Carlstedt K. Dental erosion, prevalence and risk factors among a group of adolescents in Stockholm County. Eur Arch Paediatr Dent. 2018;19(1):23–31.
50. Johansson AK, Norring C, Unell L, Johansson A. Eating disorders and oral health: a matched case–control study. Eur J Oral Sci. 2012;120(1):61–8.
51. Su MJM, Tsamtsouris A, Laskou M. Gastroesophageal reflux in children with cerebral palsy and its relationship to erosion of primary and permanent teeth. J Mass Dent Soc. 2003;52(2):20–4.
52. Murakami C, Oliveira LB, Sheiham A, Nahás Pires Corrêa MS, Haddad AE, Bönecker M. Risk indicators for erosive tooth wear in Brazilian preschool children. Caries Res. 2011;45(2):121–9.
53. Wang GR, Zhang H, Wang ZG, Jiang GS, Guo CH. Relationship between dental erosion and respiratory symptoms in patients with gastro-esophageal reflux disease. J Dent. 2010;38(11):892–8.
54. Bartlett DW, Coward PY, Nikkah C, Wilson RF. The prevalence of tooth wear in a cluster of adolescent schoolchildren and its relationship with potential explanatory factors. Br Dent J. 1998;184(3):125–9.
55. Hermont AP, Oliveira PA, Martins CC, Paiva SM, Pordeus IA, Auad SM. Tooth erosion and eating disorders: a systematic review and meta-analysis. PLoS One. 2014;9(11):e111123.
56. Arnadottir IB, Saemundsson SR, Holbrook WP. Dental erosion in Iceland teenagers in relation to dietary and lifestyle factors. Acta Odontol Scand. 2003;61(1):25–8.
57. Ganss C, Klimek J, Giese K. Dental erosion in children and adolescents--a cross-sectional and longitudinal investigation using study models. Community Dent Oral Epidemiol. 2001;29(4):264–71.
58. Mangueira DF, Sampaio FC, Oliveira AF. Association between socioeconomic factors and dental erosion in Brazilian schoolchildren. J Public Health Dent. 2009;69(4):254–9.
59. Al-Dlaigan YH, Shaw L, Smith A. Dental erosion in a group of British 14-year-old, schoolchildren. Part I: prevalence and influence of differing socioeconomic backgrounds. Br Dent J. 2001;190(3):145–9.
60. Truin GJ, Van Rijkom HM, Mulder J, Van't Hof MA. Caries trends 1996-2002 among 6- and 12-year-old children and erosive wear prevalence among 12-year-old children in The Hague. Caries Res. 2005;39(1):2–8.
61. Peres KG, Armênio MF, Peres MA, Traebert J, De Lacerda JT. Dental erosion in 12-year-old schoolchildren: a cross-sectional study in Southern Brazil. Int J Paediatr Dent. 2005;15(4):249–55.
62. El Aidi H, Bronkhorst EM, Truin GJ. A longitudinal study of tooth erosion in adolescents. J Dent Res. 2008;87(8):731–5.
63. Arnadottir IB, Holbrook WP, Eggertsson H, Gudmundsdottir H, Jonsson SH, Gudlaugsson JO, Saemundsson SR, et al. Prevalence of dental erosion in children: a national survey. Community Dent Oral Epidemiol. 2010;38(6):521–6.
64. Loureiro LA, Fager AF, Alves LS, Vaz RA, Maltz M. Erosive tooth wear among 12-year-old schoolchildren: a population-based cross-sectional study in Montevideo, Uruguay. Caries Res. 2015;49(3):216–25.
65. Künzel W, Cruz MS, Fischer T. Dental erosion in Cuban children associated with excessive consumption of oranges. Eur J Oral Sci. 2000;108(2):104–9.
66. Kirthiga M, Poornima P, Praveen R, Sakeena B, Disha P. Dental erosion and its associated factors in 11-16-year old school children. J Clin Pediatr Dent. 2015;39(4):336–42.
67. Bardsley PF, Taylor S, Milosevic A. Epidemiological studies of tooth wear and dental erosion in 14-year-old children in North West England. Part 1: the relationship with water fluoridation and social deprivation. Br Dent J. 2004;197(7):413–6.
68. Gambon DL, Brand HS, Veerman EC. Dental erosion in the 21st century: what is happening to nutritional habits and lifestyle in our society? Br Dent J. 2012;213(2):55–7.
69. McGuire J, Szabo A, Jackson S, Bradley TG, Okunseri C. Erosive tooth wear among children in the United States: relationship to race/ethnicity and obesity. Int J Paediatr Dent. 2009;19(2):91–8.
70. Salas MMS, Vargas-Ferreira F, Ardenghi TM, Peres KG, Huysmans MD, Demarco FF. Prevalence and associated factors of tooth erosion in 8–12-Year-Old Brazilian Schoolchildren. J Clin Pediatr Dent. 2017;41(5):343–50.
71. Millward A, Shaw L, Smith A. Dental erosion in four-year-old children from differing socioeconomic backgrounds. ASDC J Dent Child. 1994;61(4):263–6.
72. Mantonanaki M, Koletsi-Kounari H, Mamai-Homata E, Papaiaonnau W. Dental erosion prevalence and associated risk indicators among preschool children in Athens, Greece. Clin Oral Invest. 2013;17(2):585–93.
73. Margaritis V, Mamai-Homata E, Koletsi-Kounari H, Polychronopoulou A. Evaluation of three different scoring systems for dental erosion: a comparative study in adolescents. J Dent. 2011;39(1):88–93.
74. Milosevic A, Young PJ, Lennon MA. The prevalence of tooth wear in 14-year-old school children in Liverpool. Community Dent Health. 1994;1(2):83–6.
75. Muller-Bolla M, Courson F, Smail-Faugeron V, Bernardin T, Lupi-Pégurier L. Dental erosion in French adolescents. BMC Oral Health. 2015;15:147.
76. Järvinen V, Rytömaa I, Meurman JH. Location of dental erosion in a referred population. Caries Res. 1992;26(5):391–6.
77. Berg-Beckhoff G, Kutschmann M, Bardehle D. Methodological considerations concerning the development of oral dental erosion indexes: literature survey, validity and reliability. Clin Oral Invest. 2008;12(suppl 1):51–8.
78. Eccles JD. Dental erosion of nonindustrial origin. A clinical survey and classification. J Prosthet Dent. 1979;42(6):649–53.

79. Smith BG, Knight JK. An index for measuring the wear of teeth. Br Dent J. 1984;156(12):435–8.
80. Lussi A, Schaffner M, Hotz P, Suter P. Dental erosion in a population of Swiss adults. Community Dent Oral Epidemiol. 1991;19(5):286–90.
81. O'Brien M. Children's dental health in the United Kingdom 1993. Office of Population Censuses and Surveys. London: HMSO. p. 1994.
82. O'Sullivan EA. A new index for the measurement of erosion in children. Eur J Paed Dent. 2000;2(1):69–74.
83. Bartlett D, Ganss C, Lussi A. Basic Erosive Wear Examination (BEWE): a new scoring system for scientific and clinical needs. Clin Oral Investig. 2008;12(Suppl 1):S65–8.
84. Corica A, Caprioglio A. Meta-analysis of the prevalence of tooth wear in primary dentition. Eur J Paediatr Dent. 2014;15(4):385–8.
85. Gatou T, Mamai-Homata E. Tooth wear in the deciduous dentition of 5–7-year-old children: risk factors. Clin Oral Invest. 2012;16(3):923–33.
86. Van't Spjjker A, Rodriguez JM, Kreulen CM, Bronkhorst EM, Bartlett DW, Creugers NH. Prevalence of tooth wear in adults. Int J Prosthodont. 2009;22(1):35–42.
87. Salas MM, Nascimento GG, Huysmans MC, Demarco FF. Estimated prevalence of erosive tooth wear in permanent teeth of children and adolescents: an epidemiological systematic review and meta-regression analysis. J Dent. 2015;43(1):42–50.
88. Nayak SS, Ashokkumar BR, Ankola AV, Hebbal MI. Dental erosion among 12 year old school children in Belgaum city – a cross-sectional study. Pakistan Paediatr J. 2009;33(1):48–57.
89. Kumar S, Acharya S, Mishra P, Debnath N, Vasthare R. Prevalence and risk factors for dental erosion among 11-to-14-year-old school children in South India. J Oral Sci. 2013;55(4):329–36.
90. Brusius CD, Alves LS, Susin C, Malt M. Dental erosion among South Brazilian adolescents: a 2.5-year longitudinal study. Community Dent Oral Epidemiol. 2018;46(1):17–23.
91. Vargas-Ferreira F, Piovesan C, Praetzel JR, Mendes FM, Allison PJ, Ardenghi TM. Tooth erosion with low severity does not impact child oral health-related quality of life. Caries Res. 2010;44(6):531–9.

Further Reading

Lussi A. Dental erosion: from diagnosis to therapy. monograph in oral science. Basel: Karger; 2006.

Tooth Loss

Jun Aida

Contents

13.1 Introduction – 224

13.2 Distribution of Tooth Loss – 224
13.2.1 Prevalence and Incidence of Tooth Loss – 224
13.2.2 Distribution of the Number of Remaining Teeth – 225
13.2.3 Distribution of the Burden of Tooth Loss – 226

13.3 Measurements of Tooth Loss – 226
13.3.1 Dental Examination and Self-Reported Measurements – 226
13.3.2 Validity of Self-Reported Measurements – 227
13.3.3 Categorization of Status of Remaining Teeth – 228

13.4 Risk Factors/Predictors for Tooth Loss – 228
13.4.1 Proximal Factors for Tooth Loss – 228
13.4.2 Intermediate Factors for Tooth Loss – 229
13.4.3 Distal Factors for Tooth Loss – 230

13.5 Conclusion – 231

References – 231

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_13

Learning Objectives

- Prevalent nature of tooth loss and its burden
- Measurements for tooth loss including self-reported questionnaires
- Proximal, intermediate, and distal risk factors/predictors for tooth loss

13.1 Introduction

Tooth loss is the result of life-course experiences of dental conditions such as caries, periodontal disease, dental trauma, as well as dental treatment. After permanent dentition is completed in childhood, teeth are exposed to the effects of health-related behaviors and social determinants. Chronic exposure to these factors can cause tooth loss. Continuous tooth loss can lead to partial edentulism and eventually to complete edentulism.

As the mouth has broad physical and social functions, tooth loss substantially deteriorates the quality of life and general health status. Tooth loss impairs masticatory function [1], which reduces food intake and nutritional status, though previous reports on tooth loss-related nutrition are inconsistent [2, 3]. Instead of causing malnutrition, poor quality of food intake due to tooth loss can increase the risk of obesity [4]. In relation to social functions of oral health, tooth loss also reduces oral health-related quality of life (OHRQoL) which includes oral functions such as eating, speaking, smiling, sleeping, and contact with other people [5]. Tooth loss causes a decline of this wide range of oral functions. Therefore, having fewer remaining teeth exacerbates general health status. For example, older people with fewer remaining teeth have deteriorations in sleep [6] and mental health [7] and exhibit increased risk for becoming homebound [8]. Further, having fewer remaining teeth increases the risk for all-cause mortality [9, 10]. The presence of remaining teeth possibly increases healthy life expectancy [11].

Because of these effects on physical and social functions, the burden of tooth loss is substantial and is greatest in oral conditions [12, 13]. Based on the Global Burden of Disease (GBD) study in 2015, loss of healthy life years estimated by disability-adjusted life years (DALYs) due to total tooth loss was 7.6 million DALYs which were higher than that for caries and periodontal disease [12]. As this estimation does not include the widespread effects of tooth loss on general health status, the overall impact of tooth loss is likely to exceed this estimation. This important oral condition is relatively prevalent. In addition, there are large inequalities in the distribution of tooth loss. Wider range of risk factors explain these distributions of tooth loss.

13.2 Distribution of Tooth Loss

Oral disease and related conditions are extremely prevalent. Untreated dental caries in permanent teeth is the most prevalent disease in the world [12, 13]. Also in other oral diseases, tooth loss is highly prevalent. This section describes the distribution of tooth loss and its burden in society.

13.2.1 Prevalence and Incidence of Tooth Loss

Based on the Global Burden of Disease (GBD) study in 2015, the age-standardized prevalence of total tooth loss was 4.1%, affecting 276 million people worldwide [12]. Among 310 diseases and injuries, edentulism and severe tooth loss were the 28th most prevalent condition, whereas permanent caries was the most prevalent.

The prevalence of tooth loss increases with age. However, its incidence peaks at around age 65 (◘ Fig. 13.1) [14]. ◘ Figure 13.1 shows the prevalence and incidence of severe tooth loss defined as having fewer than nine remaining permanent teeth including edentulism. The 2015 GDB study depicts these statistics by country. ◘ Figure 13.1 shows the prevalence and incidence in regions with higher (Asia, East) and lower (Latin America, Tropical) prevalence/incidence in 1990 and 2010. In both regions, tooth loss is prevalent, especially among people 60 years or older. However, the incidence of tooth loss decreases from around age 65. These trends were similar in 1990 and 2010, although the prevalence and incidence of tooth loss decreased in 2010. In 1990, the global age-standardized prevalence of severe tooth loss was 4.4% which decreased to 2.4% in 2010. Despite the decline of tooth loss in 2010, the prevalence and incidence in higher regions were still higher than those in lower regions in 1990 (◘ Fig. 13.1).

These inequalities were notable when considered based on the country. Age-standardized prevalence of severe tooth loss was 1.5% in China and 3.9% in Brazil [14]. Countries with significantly higher prevalence compared to the global mean in 2010 were Brazil, Turkey, Iran, Mexico, and New Zealand. In contrast, the prevalence was lower in China, Japan, Nigeria, Sri Lanka, and Sweden. Tooth loss is more prevalent in women than in men, but gender differences were small in 2010 [14].

◘ Figure 13.2 shows the prevalence of edentulous people among the population aged 65–74 years old in 15 countries [15]. Overall, 13.8% of the older population was edentulate in these countries. Also in the inequalities in severe tooth loss between regions mentioned

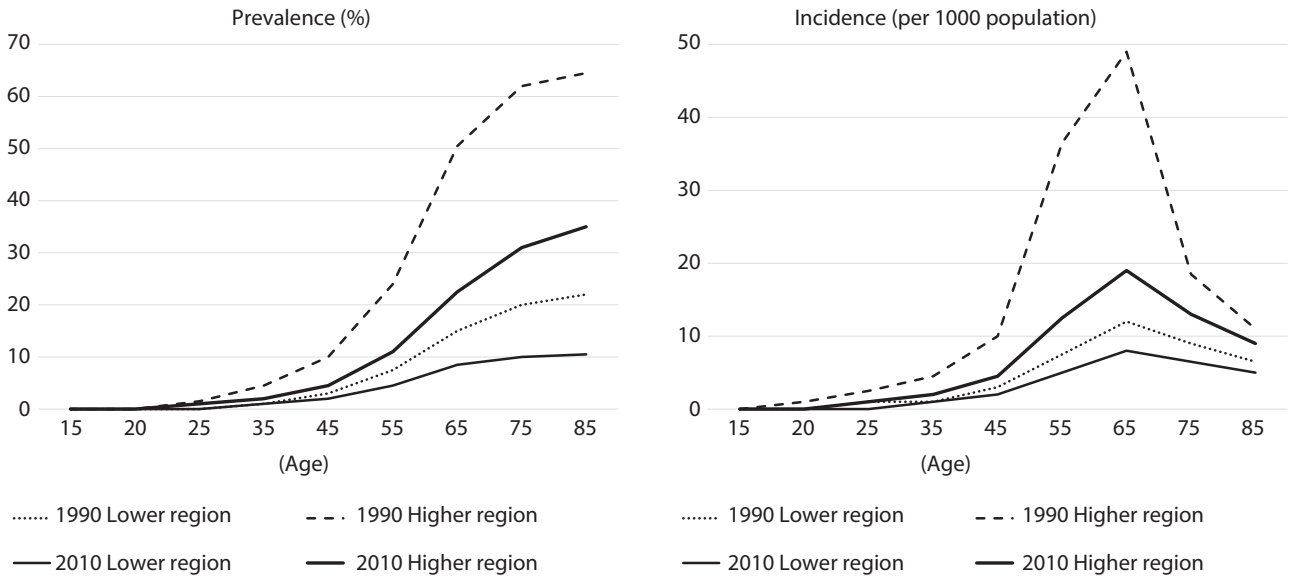


Fig. 13.1 Lower and higher regions' prevalence (%) and incidence (per 1000 population) of severe tooth loss in 1990 and 2010 by age [14]

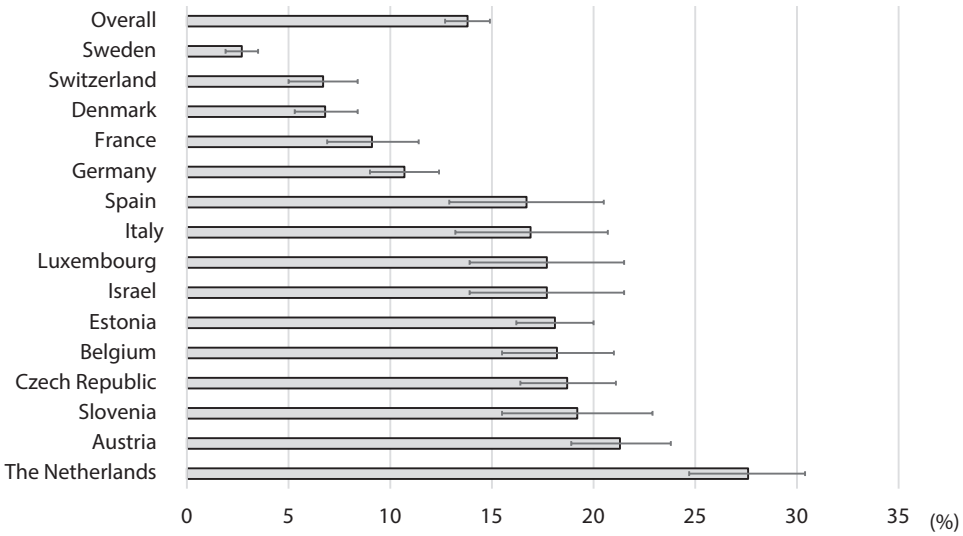


Fig. 13.2 Prevalence (%) and 95% confidence interval of edentulous people in population aged 65–74 years old [15]

above, there was a substantial difference in the prevalence of edentulous people between countries (2.7% in Sweden and 27.6% in the Netherlands).

13.2.2 Distribution of the Number of Remaining Teeth

The number of remaining teeth is also used as a measurement of tooth loss. As tooth loss frequently occurs among older people (Fig. 13.1), the mean number of remaining teeth is less among older people. Table 13.1 shows the mean number of remaining teeth among the Japanese population [16]. Almost all teeth remained in middle-aged people. However, the number of remaining teeth was less than 20 among men aged 70 years old or older and among women aged 75 years old or older.

Figure 13.3 shows the median number of natural teeth as well as natural and artificial teeth in 15 countries standardized to the European standard population [15]. The median number of natural teeth in each country varied between 15.0 in Estonia and 27.0 in Sweden. The median number of natural and artificial teeth was less varied than that of natural teeth (25.1 in Estonia and 27.3 in Austria, Denmark, Germany, Israel, Luxembourg, the Netherlands, and Switzerland).

13.2.3 Distribution of the Burden of Tooth Loss

The disease burden of tooth loss is greatest among oral conditions [12, 13]. Loss of remaining teeth exacerbates various oral functions including eating, speaking, smiling, sleeping, and contact with other people [5]. The GBD study compares disease burdens between different diseases and conditions. Years lived with disability due to total tooth loss estimated from age-standardized DALY rate (per 100,000 person-years) in 2015 were 113 for total tooth loss, which is higher than that for periodontal disease (49 DALY rate), untreated caries in permanent teeth (24 DALY rate), and untreated deciduous caries (2 DALY rate) [12]. The burden of tooth loss was greater in countries with larger aged populations. Figure 13.4 shows the distribution of burden of tooth loss indicated by years lived with disability (YLD) rate per 1000 population due to severe tooth loss including edentulism. The burden of tooth loss increases rapidly by age. In 2015, the global average burden which includes data on different population-aging countries was slightly lower than that in 1990.

Table 13.1 Mean number of remaining teeth among Japanese by age group [16]

Age group (years)	Men	Women
40–44	28.0	28.0
45–49	27.6	27.6
50–54	25.8	26.8
55–59	24.5	25.9
60–64	23.7	24.0
65–69	21.5	21.7
70–74	18.6	20.7
75–79	18.5	17.6
80–84	15.1	15.5
85	12.0	9.5

13.3 Measurements of Tooth Loss

Tooth loss is relatively easy to measure compared to dental caries or periodontal disease. Self-report questionnaires for tooth loss are widely used in questionnaire-based surveys, even in non-dental-oriented surveys [11, 15, 17], due to their simple but effective nature. This section introduces measurements of tooth loss.

13.3.1 Dental Examination and Self-Reported Measurements

When measuring tooth loss, the clinical dental examination of remaining teeth status and self-reported tooth status are widely used. Clinical dental examination is accurate and often used in relatively small-scale clinical studies. Self-reported measurements are used in self-reported questionnaires or interview surveys. Self-reported measurements are less accurate compared to

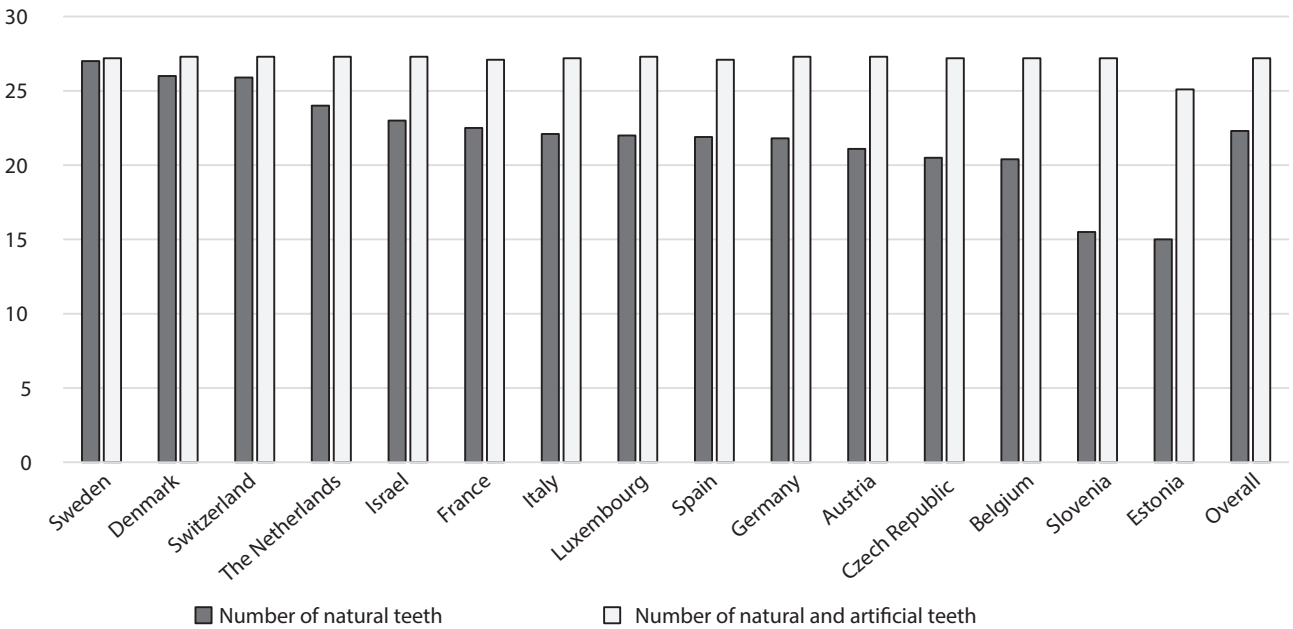


Fig. 13.3 Median number of natural teeth as well as natural and artificial teeth in 15 countries in a standardized population [15]

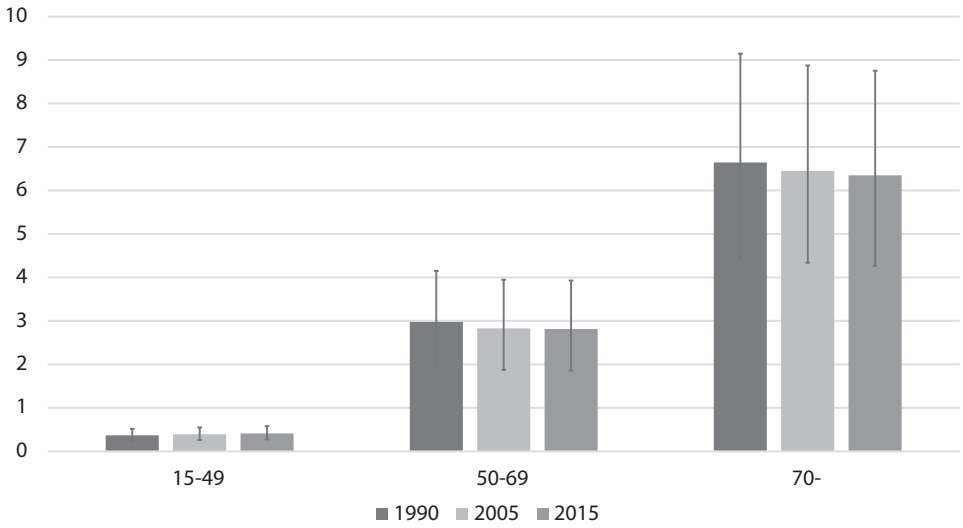


Fig. 13.4 Years lived with disability (YLD) rates per 1000 population due to severe tooth loss including edentulism [12]

dental examination. However, they cost less than clinical dental examination; therefore, self-reported measurements are often used in large-scale epidemiological studies. Self-reported questionnaires are also easily added into non-dental-oriented epidemiological studies [11, 15, 17].

For self-reported measurements related to tooth loss, several questions concerning the number of remaining teeth or experience of tooth loss are used as follows [18]: "How many natural teeth do you have in your mouth now?" [19], "Do you still have some of your own teeth? If you do, how many teeth do you have?" [20], "Dental conditions: a) All my teeth are remaining; b) I have one or two single teeth missing and not replaced; c) I have several teeth missing and not replaced; d) All my teeth are missing, but I wear no dentures." [21], and "Have you lost any teeth or had any teeth removed since we visited you about 6 months ago?" [22]. In the oral health questionnaire shown in the oral health survey method published by the World Health Organization (WHO), the number of remaining teeth is assessed by asking "How many natural teeth do you have?" with four choices: "No natural teeth," "1–9 teeth," "10–19 teeth," and "20 teeth or more" [23]. This categorization enables the detection of edentate individuals and estimation of the number of remaining teeth. This question also enables the detection of people with 10 or 20 or more teeth. This type of question and categorization seemed to effectively summarize oral health status especially for older people; therefore, it has been used in several non-dental-oriented surveys for older people [11, 24].

13.3.2 Validity of Self-Reported Measurements

To investigate whether self-reported measurements accurately reflect exact tooth status, validation studies have been conducted [18–22, 25–27]. These studies showed a significant correlation between self-reported measurements of tooth loss or the number of remaining teeth and clinical dental examination. Therefore, self-reported measurements of tooth loss and the number of remaining teeth are considered valid measurements. Because of its simple nature, the validity of self-reported tooth loss measurements is higher than that for other oral diseases. Indeed, a review reported that the validity of self-reported number of remaining teeth was higher than that for self-reported periodontal status [18].

Although self-reported measurements are considered valid, there is the possibility of misclassification in self-reported measurements of tooth loss. Therefore, research should elucidate the nature of this information bias when using self-reported measurements of tooth loss in epidemiological studies. With regard to self-reported tooth loss during a 48-month period, there were no differences between self-reported and clinical measurements [22]. In descriptive statistics of number of remaining teeth, differences in self-reported and clinical examination of number of remaining teeth are small [25–27]. Although social desirability bias may occur, in which people report having more teeth than they actually do, differences of the direction between self-reported and clinical examination (self-reported measurements being higher or lower than clinical examination) are inconsistent between studies [25–27].

When considering the bias in the studies examining the association of the number of remaining teeth on general health condition, because of the misclassification, it is supposed that confidence interval of the estimation of the association of teeth on general health is considered to become wider. If the association is statistically significant despite wider confidence intervals due to self-reported measurements in the absence of non-

differential misclassification, the association is considered to be robust. Therefore, self-reported measurements of tooth loss are still considered as useful and are used when examining the association between tooth loss and general health status [9].

13.3.3 Categorization of Status of Remaining Teeth

The degree of tooth loss can be described using continuous variables (mean or median values as shown in Table 13.1 and Fig. 13.3) or categorical variables. Depending on the purpose of the study, percentages of people with 0, 10 or more, or 20 or more teeth (i.e., prevalence of edentulous persons shown in Fig. 13.2) are often used when evaluating oral health status of the population. Practically, when using self-reported questionnaires, categorical choices of the number of remaining teeth are easier to answer than the actual number of remaining teeth. Further, there are categorizations of remaining teeth based on oral health function. This section explores the categorization of tooth loss.

Having 20 or 21 teeth is used as a categorization of remaining teeth. In the Global Goals for Oral Health 2020 by the World Dental Federation (FDI) and WHO, having 21 or more natural teeth is regarded as functional dentition [28]. Meanwhile, many studies have reported the importance of maintaining 20 or more teeth for oral health function [29, 30]. In a recently published oral health questionnaire by the WHO, the number of remaining teeth was assessed by asking "How many natural teeth do you have?". Responses were categorized into four classes: "No natural teeth," "1–9 teeth," "10–19 teeth," and "20 teeth or more" [23]. Therefore, having 20 or more teeth was measured using this question. There are health policies using having 20 or more teeth as a health goal. In Japan, having 20 or more natural teeth has been used as a goal of oral health policy since 1989, termed the "8020 (Eighty-Twenty) campaign" [31].

In the GBD study, "severe tooth loss" was defined as having zero to nine remaining teeth [14]. This categorization was derived from evidence that the diets of people with fewer than ten teeth were significantly affected, leading to malnutrition or obesity [14, 32, 33]. The above question posed by WHO also enabled the detection of those with nine or fewer teeth. Because the association between the number of remaining teeth and oral function has dose-response relationship, asking the number of teeth by several categories such as WHO's question is reasonable.

As chewing ability is affected by the number of remaining teeth as well as teeth occlusion, researches have focused on functional tooth status relating to occlusion [34–37]. The number of occluding posterior teeth is typically measured in consideration of natural teeth [34] and both natural and restored teeth [35]. With regard to functional teeth unit (FTU), pairs of occluding natural, restored, or fixed-prosthetic posterior teeth are analyzed; premolars and molars have the weight of 1 and 2 units, respectively [35]. To avoid chewing difficulties, maintaining 8–9 FTU (of the maximum 12 FTU) is recommended [36, 37].

13.4 Risk Factors/Predictors for Tooth Loss

The concept of social determinants of health is applicable to risk factors/predictors for tooth loss [38, 39]. Tooth loss is the final consequence of dental diseases such as caries and periodontal disease. Proximal causes of tooth loss are caused by intermediate risk factors including oral health status, individual characteristics, and health behaviors. Because social and environmental factors affect lifestyle and dental diseases, they are considered distal causes of tooth loss. Studies examining risks for tooth loss include reports on tooth extraction at dental clinics, reviews of dental records, and epidemiological studies [40]. Various cross-sectional and cohort studies have examined risk factors/predictors for tooth loss and factors affecting the number of remaining teeth. Several proximal, intermediate, and distal risk factors are modifiable for reducing tooth loss. In this section, various risk factors for tooth loss are discussed.

13.4.1 Proximal Factors for Tooth Loss

As the most tooth loss in permanent dentition is considered to occur in dental clinics as tooth extraction, determining the reasons for tooth extractions provides important clues regarding risks for tooth loss. Studies (predominantly cross-sectional) have reported reasons for tooth extraction in dental clinics and described the most proximal risks for tooth loss [41–46].

As the most direct causes of tooth loss, caries, periodontal disease, prosthetic and orthodontic treatment, dental trauma, dental pain due to endodontic and periapical disease, wisdom teeth, and patient request have been reported [42, 47]. Caries is considered the most important factor for tooth loss; caries and its sequelae along with periodontal disease are major reasons for tooth extraction [40–47]. Figure 13.5 shows the distribution of reasons for tooth loss among postmenopausal women during a 5-year follow-up study in Buffalo, United States [48]. Caries is the major reason for tooth loss following periodontal disease and other diseases.

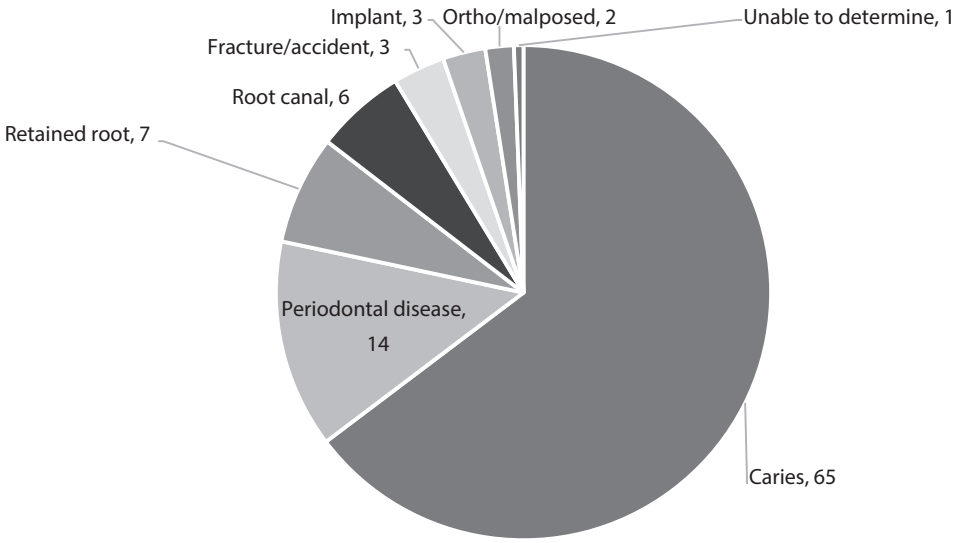


Fig. 13.5 Reasons for tooth loss among postmenopausal women during a 5-year follow-up study in the United States [48]

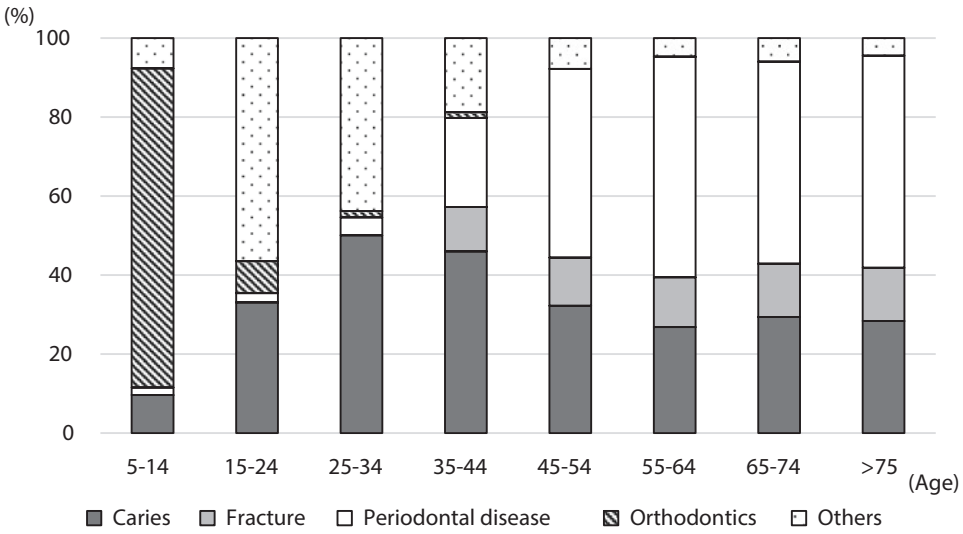


Fig. 13.6 Reasons for tooth extraction by age in Japan [46]

Proportions of the reasons for tooth extraction are different between studies. Percentages of tooth extraction due to caries and its sequelae and periodontal disease were 70.3% and 15.1% in Brazil [42], 51% and 21% in Scotland [43], 51% and 14.4% in Iran [44], and 54.1% and 16.5% in Nigeria, respectively [45]. When comparing different time periods, caries and its sequelae (fracture) and periodontal disease were 43.3% and 41.8% in 2005 [46] and 47.0% and 37.1% in 2018 in Japan [49], respectively.

Reasons for tooth loss also differ by age [43, 46]. Figure 13.6 shows the reasons for tooth extraction by age in Japan in 2005 [46]. Caries and fractures (most fractures are due to sequelae of caries) were common across all age groups, whereas periodontal disease increased after middle age.

13.4.2 Intermediate Factors for Tooth Loss

Several factors affect the direct causes of tooth loss mentioned above. For example, smoking behavior causes periodontal disease, and severe periodontitis causes tooth loss. Cohort studies following baseline characteristics up until tooth loss report risk factors/predictors for tooth loss. This section discusses intermediate factors influencing tooth loss such as oral health status, individual characteristics, and health behaviors.

Individuals' demographic and general health characteristics are associated with tooth loss. Older age predicts a higher risk for tooth loss [44, 50–52]. Regarding general health condition, diabetes is considered a risk for tooth loss [48, 53, 54]. Several studies report that women have higher risk than men for tooth loss [14, 50,

55], but there are exceptions as shown in Table 13.1 [16, 44]. Osteoporosis may explain the higher risk for tooth loss among women, although conclusive evidence is lacking [56]. Although bidirectional relationships are supposed, the association of tooth loss on obesity [4, 48] and metabolic syndrome [55] has been reported.

Oral diseases or poor oral conditions, especially periodontal disease and previous tooth loss, are considered risk factors or predictors of future tooth loss [48, 50–52]. Plaque, calculus [48], and dental caries may increase the risk of tooth loss [50–52]. Removal of partial dentures increases risk of future tooth loss, but this risk can be reduced by dental visits for periodontal maintenance [57]. In regard to tooth type, molars are the most frequently extracted tooth, although tooth type itself is not indicative of oral health status [41, 42, 47, 52]. For example, the percentages of extracted teeth of mandibular anterior and posterior teeth are 9.2% and 90.8%, respectively, in Northwestern Nigeria [45]; those in maxillary anterior and posterior teeth are 24.1% and 75.9%, respectively. In Japan, percentages of extracted mandibular anterior and posterior teeth are 24.3% and 75.7%, respectively [46]. In maxillary anterior and posterior teeth, the percentages are 31.4% and 68.6%, respectively.

Health behaviors related to caries and periodontal disease are also risk factors for tooth loss. Smoking [50, 52], infrequent dental visits [44, 52, 53], shorter tooth brushing time [58], infrequent dental floss use [55], and frequent intake of sweets [58] are considered as behavioral risk factors for tooth loss. Because deficiencies in vitamins and other nutrients increase the risk of periodontal disease, they may also increase the risk of tooth loss [59].

13.4.3 Distal Factors for Tooth Loss

Various social determinants affect behavior and population health [38, 39]. Proximal and intermediate factors for tooth loss mentioned above are also affected by social determinants. This section describes distal factors influencing tooth loss.

Socioeconomic status is frequently associated with tooth loss, as oral health inequalities are considered an emerging global health issue [60]. When evaluating social inequalities in health, associations between socioeconomic status and health outcomes are evaluated [61]. Previous studies have reported an association between poor socioeconomic conditions and increased risk of tooth loss or having fewer remaining teeth. Studies have used various proximal measurements of socioeconomic status such as income/economic condition [52, 62, 63], social deprivation [64], education [50, 55, 65], and occupation [66]. Theoretically, there are several possible relationships between socioeconomic condition and oral health [67]: poorer economic conditions restricting access to dental care [68]; health deteriorating behaviors are clustering among people with poorer socioeconomic condition [69]; and psychosocial stress-mediating associations between socioeconomic status and tooth loss [64]. These effects accumulate throughout the life-course [70]. Studies have confirmed the association between socioeconomic status and tooth loss using a robust causal-inference technique [62, 65].

As behaviors and health are affected by neighbors, social relationships are considered social determinants of tooth loss. Behaviors relating to oral diseases such as smoking and eating spread through social networks [71, 72]. Studies have reported associations between rich social networks and more remaining teeth [58]. As having friends with diverse backgrounds increases informational channels, social network diversity is also associated with the number of remaining teeth [73].

In addition to social conditions, community social environments also affect oral health. As shown in Figs. 13.2 and 13.3, there are substantial inequalities in tooth status between countries. Health inequalities between communities and/or countries are explained by differences in individual characteristics of residents as well as social environments in each region. Where we live influences our behaviors and oral health. For example, residents in communities with water fluoridation have a lower risk of tooth loss [74]. A high density of dental clinics, a proxy for geographical accessibility of dental care, is associated with more remaining teeth [75]. Alongside geographical accessibility, welfare state regimes also influence access to dental care. A study comparing welfare state regimes and tooth loss reported that the Scandinavian regime showed the lowest prevalence of tooth loss, while the Eastern regime showed the highest prevalence [76]. Regardless of individual economic conditions, people living in wealthy communities [77] or communities with smaller income inequality [78] have a lower risk of tooth loss. Living in communities with rich social capital ("resources that are accessed by individuals as a result of their membership of a network or a group" [79]) may also reduce the risk of tooth loss [80]. These community-level social environments affect both intermediate and proximal risks for tooth loss, thereby altering the probability of tooth loss.

Summary of Risk Factors/Predictors for Tooth Loss

Table 13.2 summarizes the risk factors/predictors for tooth loss. From individuals to society, a variety of factors influence tooth loss after teeth eruption. Some factors are modifiable and can reduce the risk of tooth loss. Throughout the life-course, prevention of oral diseases, changes in oral health behaviors, and

improvement of social environment may contribute to maintaining natural teeth at an older age. From the perspective of social determinants of health, to avoid "victim blaming," upstream approaches that focus on distal factors are required for reducing inequalities in tooth loss [81].

Table 13.2 Summary of risk factors/predictors for tooth loss

Proximal factors	Caries, periodontal disease, prosthetic and orthodontic treatment, dental trauma, dental pain, wisdom teeth, patient request
Intermediate factors	Age, diabetes: Oral health; plaque, calculus, periodontal disease, previous tooth loss: Health behaviors; smoking, dental visit, brushing, flossing, intake of sweets foods/beverages
Distal factors	Socioeconomic status, water fluoridation, accessibility for dental care (geographical, welfare state regime), social relationships, social capital, social inequalities

13.5 Conclusion

Tooth loss is the final consequence of poor oral health behaviors and oral diseases throughout the life-course. Tooth loss substantially deteriorates the quality of life and general health status. To measure tooth loss, clinical dental examination and self-reported questionnaires are used. There are various proximal, intermediate, and distal factors influencing tooth loss. Caries and periodontal disease are major proximal causes for tooth loss. Health behaviors and health conditions such as diabetes are known to be intermediate risk factors for tooth loss. Socioeconomic status and social environmental factors such as fluoridated water supply, accessibility of dental care, and social capital affect tooth loss as distal factors. Prevention of oral diseases, changes in oral health behaviors, and improvement of the social environment may reduce the risk of tooth loss.

Points of Emphasis

- Tooth loss, the final consequence of oral health behaviors and oral diseases, causes the greatest burden in oral conditions.
- Tooth loss is relatively easy to measure in clinical dental examination and self-reported questionnaires.
- There are various proximal, intermediate, and distal factors influencing tooth loss.
- Prevention of oral diseases, changes in oral health behaviors, and improvement of the social environment may reduce the risk of tooth loss.

References

1. Naka O, Anastassiadou V, Pissiotis A. Association between functional tooth units and chewing ability in older adults: a systematic review. Gerodontology. 2014;31(3):166–77.
2. Gaewkhiew P, Sabbah W, Bernabe E. Does tooth loss affect dietary intake and nutritional status? A systematic review of longitudinal studies. J Dent. 2017;67:1–8.
3. Tada A, Miura H. Systematic review of the association of mastication with food and nutrient intake in the independent elderly. Arch Gerontol Geriatr. 2014;59(3):497–505.
4. Nascimento GG, Leite FR, Conceicao DA, Ferrua CP, Singh A, Demarco FF. Is there a relationship between obesity and tooth loss and edentulism? A systematic review and meta-analysis. Obes Rev. 2016;17(7):587–98.
5. Tan H, Peres KG, Peres MA. Retention of teeth and oral health-related quality of life. J Dent Res. 2016;95(12):1350–7.
6. Koyama S, Aida J, Cable N, Tsuboya T, Matsuyama Y, Sato Y, et al. Sleep duration and remaining teeth among older people. Sleep Med. 2018;52:18–22.
7. Yamamoto T, Aida J, Kondo K, Fuchida S, Tani Y, Saito M, et al. Oral health and incident depressive symptoms: JAGES project longitudinal study in older Japanese. J Am Geriatr Soc. 2017;65(5):1079–84.
8. Koyama S, Aida J, Kondo K, Yamamoto T, Saito M, Ohtsuka R, et al. Does poor dental health predict becoming homebound among older Japanese? BMC Oral Health. 2016;16(1):51.
9. Peng J, Song JK, Han J, Chen Z, Yin X, Zhu J, et al. The relationship between tooth loss and mortality from all causes, cardiovascular diseases and coronary heart disease: systematic review and dose-response meta-analysis. Biosci Rep. 2019;39(1):BSR20181773.
10. Koka S, Gupta A. Association between missing tooth count and mortality: a systematic review. J Prosthodont Res. 2018;62(2):134–51.
11. Matsuyama Y, Aida J, Watt RG, Tsuboya T, Koyama S, Sato Y, et al. Dental status and compression of life expectancy with disability. J Dent Res. 2017;96(9):1006–13.
12. Kassebaum NJ, Smith AGC, Bernabe E, Fleming TD, Reynolds AE, Vos T, et al. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990-2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96(4):380–7.
13. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545–602.
14. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe tooth loss: a systematic review and meta-analysis. J Dent Res. 2014;93(7 suppl):20S–8S.
15. Stock C, Jurges H, Shen J, Bozorgmehr K, Listl S. A comparison of tooth retention and replacement across 15 countries in the over-50s. Community Dent Oral Epidemiol. 2016;44(3):223–31.
16. Ministry of Health, Labour and Welfare. Report on the survey of dental diseases 2016. Tokyo: Ministry of Health, Labour and Welfare; 2017.

17. Tsakos G, Watt RG, Rouxel PL, de Oliveira C, Demakakos P. Tooth loss associated with physical and cognitive decline in older adults. J Am Geriatr Soc. 2015;63(1):91–9.
18. Ramos RQ, Bastos JL, Peres MA. Diagnostic validity of self-reported oral health outcomes in population surveys: literature review. Rev Bras Epidemiol. 2013;16(3):716–28.
19. Pitiphat W, Garcia RI, Douglass CW, Joshipura KJ. Validation of self-reported oral health measures. J Public Health Dent. 2002;62(2):122–8.
20. Axelsson G, Helgadottir S. Comparison of oral health data from self-administered questionnaire and clinical examination. Community Dent Oral Epidemiol. 1995;23(6):365–8.
21. Palmqvist S, Soderfeldt B, Arnbjerg D. Self-assessment of dental conditions: validity of a questionnaire. Community Dent Oral Epidemiol. 1991;19(5):249–51.
22. Gilbert GH, Chavers LS, Shelton BJ. Comparison of two methods of estimating 48-month tooth loss incidence. J Public Health Dent. 2002;62(3):163–9.
23. World Health Organization. Oral health surveys: basic methods. Geneva: World Health Organization; 2013.
24. National Centre for Social Research. English longitudinal study of ageing wave seven interview questionnaire – 2014 to 2015. London: National Centre for Social Research. p. 2015. Available from: https://www.elsa-project.ac.uk/uploads/elsa/docs_w7/ELSA%20Wave%207%20Individual%20Questionnaire.pdf.
25. Matsui D, Yamamoto T, Nishigaki M, Miyatani F, Watanabe I, Koyama T, et al. Validity of self-reported number of teeth and oral health variables. BMC Oral Health. 2016;17(1):17.
26. Ueno M, Zaitsu T, Shinada K, Ohara S, Kawaguchi Y. Validity of the self-reported number of natural teeth in Japanese adults. J Investig Clin Dent. 2010;1(2):79–84.
27. Simila T, Nieminen P, Virtanen JI. Validity of self-reported number of teeth in middle-aged Finnish adults: the Northern Finland Birth Cohort Study 1966. BMC Oral Health. 2018;18(1):210.
28. Hobdell M, Petersen PE, Clarkson J, Johnson N. Global goals for oral health 2020. Int Dent J. 2003;53(5):285–8.
29. Wright FAC, Law GG, Milledge KL, Chu SK, Hsu B, Valdez E, et al. Chewing function, general health and the dentition of older Australian men: the Concord Health and Ageing in Men Project. Community Dent Oral Epidemiol. 2019;47(2):134–41.
30. Yoshihara A, Watanabe R, Nishimuta M, Hanada N, Miyazaki H. The relationship between dietary intake and the number of teeth in elderly Japanese subjects. Gerodontology. 2005;22(4):211–8.
31. Zaitsu T, Saito T, Kawaguchi Y. The oral healthcare system in Japan. Healthcare (Basel). 2018;6(3):79.
32. Sheiham A, Steele JG, Marcenes W, Lowe C, Finch S, Bates CJ, et al. The relationship among dental status, nutrient intake, and nutritional status in older people. J Dent Res. 2001;80(2):408–13.
33. Nowjack-Raymer RE, Sheiham A. Numbers of natural teeth, diet, and nutritional status in US adults. J Dent Res. 2007;86(12):1171–5.
34. van der Bilt A, Olthoff LW, Bosman F, Oosterhaven SP. The effect of missing postcanine teeth on chewing performance in man. Arch Oral Biol. 1993;38(5):423–9.
35. Hatch JP, Shinkai RS, Sakai S, Rugh JD, Paunovich ED. Determinants of masticatory performance in dentate adults. Arch Oral Biol. 2001;46(7):641–8.
36. Ueno M, Yanagisawa T, Shinada K, Ohara S, Kawaguchi Y. Masticatory ability and functional tooth units in Japanese adults. J Oral Rehabil. 2008;35(5):337–44.
37. Hsu K-J, Yen Y-Y, Lan S-J, Wu Y-M, Chen C-M, Lee H-E. Relationship between remaining teeth and self-rated chewing ability among population aged 45 years or older in Kaohsiung City, Taiwan. Kaohsiung J Med Sci. 2011;27(10):457–65.
38. Watt R, Do L, Newton T. Social determinants of oral health inequalitie. In: Social inequalities in oral health: from evidence to action [Internet]. London: UCL Research Department of Epidemiology and Public Health; 2015. p. 14–5. Available from: http://www.icohirp.com/monograph.html.
39. Patrick DL, Lee RS, Nucci M, Grembowski D, Jolles CZ, Milgrom P. Reducing oral health disparities: a focus on social and cultural determinants. BMC Oral Health. 2006;6(Suppl 1):S4.
40. Burt A, Eklund A. Tooth loss. In: Dentistry, dental practice, and the community. 6th ed. St. Louis: Elsevier Saunders; 2005. p. 223–32.
41. McCaul LK, Jenkins WM, Kay EJ. The reasons for the extraction of various tooth types in Scotland: a 15-year follow up. J Dent. 2001;29(6):401–7.
42. Caldas AF Jr. Reasons for tooth extraction in a Brazilian population. Int Dent J. 2000;50(5):267–73.
43. Chestnutt IG, Binnie VI, Taylor MM. Reasons for tooth extraction in Scotland. J Dent. 2000;28(4):295–7.
44. Jafarian M, Etebarian A. Reasons for extraction of permanent teeth in general dental practices in Tehran, Iran. Med Princ Pract. 2013;22(3):239–44.
45. Taiwo AO, Ibikunle AA, Braimah RO, Sulaiman OA, Gbotolorun OM. Tooth extraction: pattern and etiology from extreme Northwestern Nigeria. Eur J Dent. 2017;11(3):335–9.
46. Aida J, Ando Y, Akhter R, Aoyama H, Masui M, Morita M. Reasons for permanent tooth extractions in Japan. J Epidemiol. 2006;16(5):214–9.
47. Muller F, Naharro M, Carlsson GE. What are the prevalence and incidence of tooth loss in the adult and elderly population in Europe? Clin Oral Implants Res. 2007;18(Suppl 3):2–14.
48. Bole C, Wactawski-Wende J, Hovey KM, Genco RJ, Hausmann E. Clinical and community risk models of incident tooth loss in postmenopausal women from the Buffalo Osteo Perio Study. Community Dent Oral Epidemiol. 2010;38(6):487–97.
49. 8020 Promotion Foundation. The second survey of reasons for tooth extraction (in Japanese). Tokyo: 8020 Promotion Foundation; 2018. Available from: https://www.8020zaidan.or.jp/pdf/document-tooth-extraction-investigation-2nd.pdf.
50. Haworth S, Shungin D, Kwak SY, Kim HY, West NX, Thomas SJ, et al. Tooth loss is a complex measure of oral disease: determinants and methodological considerations. Community Dent Oral Epidemiol. 2018;46(6):555–62.
51. Hassel AJ, Safaltin V, Grill S, Schroder J, Wahl HW, Klotz AL, et al. Risk factors for tooth loss in middle and older age after up to 10 years: an observational cohort study. Arch Oral Biol. 2018;86:7–12.
52. Saito M, Shimazaki Y, Fukai K, Furuta M, Aida J, Ando Y, et al. Risk factors for tooth loss in adult Japanese dental patients: 8020 Promotion Foundation Study. J Invest Clin Dent. 2019;10:e12392.
53. Yoo JJ, Kim DW, Kim MY, Kim YT, Yoon JH. The effect of diabetes on tooth loss due to periodontal disease: a nationwide population-based cohort study in South Korea. J Periodontol. 2019;90(6):576–83.
54. D'Aiuto F, Gable D, Syed Z, Allen Y, Wanyonyi KL, White S, et al. Evidence summary: the relationship between oral diseases and diabetes. Br Dent J. 2017;222(12):944–8.
55. Tsai SJ, Lin MS, Chiu WN, Jane SW, Tu LT, Chen MY. Factors associated with having less than 20 natural teeth in rural adults: a cross-sectional study. BMC Oral Health. 2015;15:158.
56. Friedman PK, Lamster IB. Tooth loss as a predictor of shortened longevity: exploring the hypothesis. Periodontol 2000. 2016;72(1):142–52.
57. Tada S, Allen PF, Ikebe K, Matsuda K, Maeda Y. Impact of periodontal maintenance on tooth survival in patients with

removable partial dentures. J Clin Periodontol. 2015;42(1):46–53.
58. Aida J, Kuriyama S, Ohmori-Matsuda K, Hozawa A, Osaka K, Tsuji I. The association between neighborhood social capital and self-reported dentate status in elderly Japanese – The Ohsaki Cohort 2006 Study. Community Dent Oral Epidemiol. 2011;39(3):239–49.
59. Skoczek-Rubinska A, Bajerska J, Menclewicz K. Effects of fruit and vegetables intake in periodontal diseases: a systematic review. Dent Med Probl. 2018;55(4):431–9.
60. Watt RG, Heilmann A, Listl S, Peres MA. London charter on oral health inequalities. J Dent Res. 2016;95(3):245–7.
61. Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. Soc Sci Med. 1997;44(6):757–71.
62. Matsuyama Y, Aida J, Tsuboya T, Hikichi H, Kondo K, Kawachi I, et al. Are lowered socioeconomic circumstances causally related to tooth loss? A natural experiment involving the 2011 great East Japan earthquake. Am J Epidemiol. 2017;186(1):54–62.
63. Seerig LM, Nascimento GG, Peres MA, Horta BL, Demarco FF. Tooth loss in adults and income: systematic review and meta-analysis. J Dent. 2015;43(9):1051–9.
64. Sanders AE, Slade GD, Turrell G, Spencer AJ, Marcenes W. Does psychological stress mediate social deprivation in tooth loss? J Dent Res. 2007;86(12):1166–70.
65. Matsuyama Y, Jurges H, Listl S. The causal effect of education on tooth loss: evidence from United Kingdom schooling reforms. Am J Epidemiol. 2019;188(1):87–95.
66. Yamamoto T, Kondo K, Aida J, Fuchida S, Hirata Y, JAGES Group. Association between the longest job and oral health: Japan Gerontological Evaluation Study project cross-sectional study. BMC Oral Health. 2014;14(1):130.
67. Sisson KL. Theoretical explanations for social inequalities in oral health. Community Dent Oral Epidemiol. 2007;35(2):81–8.
68. Reda SF, Reda SM, Thomson WM, Schwendicke F. Inequality in utilization of dental services: a systematic review and meta-analysis. Am J Public Health. 2018;108(2):e1–7.
69. Sabbah W, Suominen AL, Vehkalahti MM, Aromaa A, Bernabe E. The role of behaviour in inequality in increments of dental caries among Finnish adults. Caries Res. 2015;49(1):34–40.
70. Astrom AN, Ekback G, Lie SA, Ordell S. Life-course social influences on tooth loss and oral attitudes among older people: evidence from a prospective cohort study. Eur J Oral Sci. 2015;123(1):30–8.
71. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med. 2007;357(4):370–9.
72. Christakis NA, Fowler JH. The collective dynamics of smoking in a large social network. N Engl J Med. 2008;358(21):2249–58.
73. Aida J, Kondo K, Yamamoto T, Saito M, Ito K, Suzuki K, et al. Is social network diversity associated with tooth loss among older Japanese adults? PLoS One. 2016;11(7):e0159970.
74. Sullivan VO, Connell BCO. Water fluoridation, dentition status and bone health of older people in Ireland. Community Dent Oral Epidemiol. 2015;43(1):58–67.
75. Hanibuchi T, Aida J, Nakade M, Hirai H, Kondo K. Geographical accessibility to dental care in the Japanese elderly. Community Dent Health. 2011;28(2):128–35.
76. Guarnizo-Herreno CC, Watt RG, Pikhart H, Sheiham A, Tsakos G. Socioeconomic inequalities in oral health in different European welfare state regimes. J Epidemiol Community Health. 2013;67(9):728–35.
77. Ito K, Aida J, Yamamoto T, Ohtsuka R, Nakade M, Suzuki K, et al. Individual- and community-level social gradients of edentulousness. BMC Oral Health. 2015;15(1):34.
78. Aida J, Kondo K, Kondo N, Watt RG, Sheiham A, Tsakos G. Income inequality, social capital and self-rated health and dental status in older Japanese. Soc Sci Med. 2011;73(10):1561–8.
79. Kawachi I, Berkman LF. Social capital, social cohesion, and health. In: Berkman LF, Kawachi I, Glymour MM, editors. Social epidemiology. 2nd ed. Oxford: Oxford University Press; 2014. p. 290–319.
80. Koyama S, Aida J, Saito M, Kondo N, Sato Y, Matsuyama Y, et al. Community social capital and tooth loss in Japanese older people: a longitudinal cohort study. BMJ Open. 2016;6(4):e010768.
81. Watt RG. From victim blaming to upstream action: tackling the social determinants of oral health inequalities. Community Dent Oral Epidemiol. 2007;35(1):1–11.

Further Reading

Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe tooth loss: a systematic review and meta-analysis. J Dent Res. 2014;93(7 suppl):20S–8S.

Kassebaum NJ, Smith AGC, Bernabe E, Fleming TD, Reynolds AE, Vos T, Murray CJL, Marcenes W, GBD 2015 Oral Health Collaborators. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990-2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96(4):380–7.

Ramos RQ, Bastos JL, Peres MA. Diagnostic validity of self-reported oral health outcomes in population surveys: literature review. Rev Bras Epidemiol. 2013;16(3):716–28.

Halitosis

Paulo Nadanovsky

Contents

14.1 Introduction – 236

14.2 Methods of Diagnosing-Detecting Bad Breath – 236
14.2.1 The Bad Breath Paradox – 238

14.3 Prevalence of Bad Breath – 238

14.4 Causes of Bad Breath – 239
14.4.1 Mechanisms of Bad Breath Formation – 239
14.4.2 Tongue Coating (Debris, Bacteria, and Dead Cells) – 240
14.4.3 Periodontal Disease – 240
14.4.4 Airways – 240
14.4.5 Transitory Bad Breath – 241
14.4.6 Systemic Diseases – 241
14.4.7 Gastrointestinal Diseases – 241

14.5 Treatment of Bad Breath – 241

14.6 The Experience of a Halitosis Clinic in Rio de Janeiro from 1998 to 2004 ("Clínica do Tratamento do Hálito – CTH-RJ") – 243

14.7 Conclusion – 244

References – 245

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_14

Learning Goals

- To discuss the methods of detecting bad breath
- To describe the prevalence of bad breath
- To list and describe the causes of bad breath
- To describe the treatments available for bad breath
- To share the experience of a halitosis clinic in Rio de Janeiro, regarding the detection of bad breath and the treatment of patients who sought care for their bad breath problem, and our short-term treatment results

14.1 Introduction

Halitosis or bad breath is the unpleasant odor that comes out of the mouth or nose. Many people are interested in knowing about bad breath [1] as it can cause considerable psychological and social problems. Most adults present occasional bad breath, mainly when they wake up. A smaller number of people have bad breath more constantly. The social and psychological impact of bad breath can be bigger or smaller, independently of its persistency or intensity. There is a strong psychological component that influences the way people deal with body odors in general and breath odor in particular. The preoccupation with oral malodor may be a bigger problem than the oral malodor per se [2].

This chapter was organized in four parts: the methods of diagnosing-detecting, the prevalence, the causes, and the treatment of halitosis. Narrative [3, 4, 5, 6] and systematic [7, 8, 9] reviews about these themes are available in the international scientific literature.

14.2 Methods of Diagnosing-Detecting Bad Breath

The individual is an unreliable assessor of his own breath odor. For that reason, health professionals have to be creative when diagnosing-detecting bad breath. There are four ways to diagnose-detect bad breath [10]: organoleptic assessment; volatile sulfur compound concentration assessment; the benzoyl-DL arginine-naphthylamide (BANA) test; and the electronic nose (Table 14.1). The *organoleptic assessment* is the detection of bad breath through the human nose. The dentist, doctor, or other health professional may obtain information about the presence, constancy, type, and intensity of bad breath directly from a close person to the individual, for example, his wife. Alternatively, when a close person is not available, the health professional may ask the individual whether someone close to him, either someone who lives with him or work close to him every day, relates that he constantly presents bad breath.

Table 14.1 Methods of diagnosing-detecting bad breath

Organoleptic assessment	Information from a close person about the smell of the individual's breath (directly or indirectly) Trained professional smelling the individual's breath
Volatile sulfur compounds (VSC) concentration assessment	Gas chromatography that distinguishes different types of gases Portable less expensive devices that measure the concentration of all VSC together, not specifying the different VSC types (e.g., Halimeter™)
The benzoyl-DL arginine-naphthylamide (BANA) test	Detects a component of bad breath that is independent of the VSC
The electronic nose and the artificially intelligent nose	Not used routinely in bad breath research or clinic – still in prototypical phase

Another form of organoleptic assessment is when a trained and calibrated health professional smells the breath of the individual through his mouth and nose and classifies the intensity of the malodor in a scale of 6 or 5 points. For example, in one scale the number 0 represents no odor, 1 barely noticeable odor, 2 slight odor, 3 moderate odor, 4 strong odor, and 5 extremely strong odor [11, 12]. In another scale, oral odor is classified as follows: 5 very good odor, 4 good odor, 3 moderate odor, 2 bad odor, and 1 very bad odor [13]. The main limitation of this organoleptic assessment by a professional smelling the breath of the individual is that it does not detect the constancy of the bad breath during the week and months and daily fluctuations in its intensity, as it is a one point in time assessment. The information given by close persons (directly by them or asking the individual being assessed whether a close person related that he constantly have bad breath) reflects the smell during the day, every day, week, and month. The organoleptic forms of assessing bad breath are the best method to detect and diagnose bad breath. The validity of the other methods of detection is tested against the organoleptic assessment by a trained professional who is considered the gold standard [14, 15]. Gold standard is the best current indicator of an event or disease, in this case, bad breath. Other forms of organoleptic assessment, in order to try and obtain more objective measures, have been tested. For example, Kim et al. [14] proposed the collection and enclosure of breath samples in syringes for latter independent assessment.

The main chemical compounds of bad breath are the *volatile sulfur compounds* (VSC) [15]. The best method

for the detection of these compounds is gas chromatography [16]. This technique distinguishes different types of gases. However, it is expensive and inefficient for utilization in the clinic and in field research. There are portable less expensive devices, and some of these measure the concentration of all VSC together, not specifying the different VSC types. One of these is the Halimeter™, which correctly detects the presence and absence of bad breath in approximately 50% of the times. The *BANA scores* are associated with a component of bad breath that is independent of the VSC. Therefore, BANA may complement the instrumental detection of bad breath [12]. The *electronic nose* is still in prototypical phase, not yet used routinely in bad breath research or clinic [17]. In the future, there may be artificially intelligent noses that will be able to learn to detect the different types of bad breath and identify specific origins of the odors, from the oral cavity and the other regions of the body [18].

► Box 14.1 describes the main forms of evaluating the accuracy of the methods of diagnosing-detecting bad breath.

Box 14.1 The main forms of evaluating the accuracy of the methods of diagnosing-detecting bad breath

Sensitivity: frequency of positive results among the individuals with bad breath

Specificity: frequency of negative results among the individuals without bad breath

Positive predictive value: given a positive result, what is the probability that the individual has bad breath

Negative predictive value: given a negative result, what is the probability that the individual does not have bad breath

Likelihood ratio for a positive result: how much more probable is a positive result in an individual with bad breath than a positive result in an individual without bad breath

In a dental clinic dedicated exclusively to the care of people worried about bad breath in Rio de Janeiro, Brazil, 1245 individuals received an organoleptic assessment of their breath by trained dentists (gold standard) in addition to the VSC concentration assessment with the Halimeter™. Individuals were classified as having bad breath when they scored 1 or 2 in the organoleptic assessment, that is, 1 very bad odor and 2 bad odor [13]. According to the ROC (receiver operating characteristic) curve, the most accurate Halimeter™ score, that is, the score that presented the highest sensitivity and specificity together, was 100 parts per billion (ppb). At this level, both sensitivity and specificity were nearly 75% each.

Table 14.2 shows the sensitivity and specificity for three different Halimeter™ scores: 40 ppb, 100 ppb, and 200 ppb. Ninety percent of the individuals classified as "bad breath absent" by the trained dentist smelling the breath (scores 4 good odor or 5 very good odor) obtained a Halimeter™ score lower than 200 ppb. Thus, a Halimeter™ score lower than 200 ppb is a test of high specificity and a result of 200 ppb or higher helps to rule in (confirms) the presence of bad breath. On the other hand, 90% of the individuals classified as "bad breath present" by the trained dentist smelling the breath (scores 1 very bad odor or 2 bad odor) obtained a Halimeter™ score higher than 40 ppb. Thus, a Halimeter™ score higher than 40 ppb is a test of high sensitivity and a result of 40 ppb or lower rules out (discards) the presence of bad breath.

The 100 ppb Halimeter™ score appears to be the overall best threshold to define whether a person has or does not have bad breath. However, sensitivity and specificity of 73% are relatively low, leading to nearly 50% of wrong diagnoses. Thus, it is still necessary to apply the organoleptic assessment by trained professionals and to obtain information from close persons. It is important to note that the population that generated the sensitivity and specificity values reported here was constituted by patients in a clinic dedicated exclusively to the care of people with bad breath concerns. Thus, these values may be different when calculated in a general population.

Table 14.3 is an attempt to associate different scores of the breath by trained dentists smelling the breath of the individual with a categorical classification of Halimeter™ scores. Like in other populations in previous studies, the observed association was only moderate.

Spearman correlation = 0.58 ($p < 0.01$). The Halimeter™ scores were categorized into five levels according to the quintiles of the distribution of the scores of the 1245 individuals analyzed.

Table 14.2 Sensitivity and specificity for three different Halimeter™ scores: 40 ppb, 100 ppb, and 200 ppb. Gold standard for the presence of bad breath was bad odor or very bad odor classified by trained dentists smelling the individual's breath

Halimeter™ scores	Sensitivity (%)	Specificity (%)
Lower than 40 ppb (helps rule out or discard bad breath)	90	45
100 ppb	73	73
Higher than 200 ppb (helps rule in or confirm bad breath)	52	90

Table 14.3 Association between organoleptic assessment by trained dentists smelling the individual's breath and Halimeter™ scores divided in five categories

Organoleptic assessment (trained dentists)	Halimeter™ scores
5 = very good odor (no odor)	5 = 0 a 29 ppb
4 = good odor (barely noticeable odor)	4 = 30 a 59 ppb
3 = moderate odor (moderate odor)	3 = 60 a 119 ppb
2 = bad odor (strong odor)	2 = 120 a 229 ppb
1 = very bad odor (extremely strong odor)	1 = higher than 230 ppb

14.2.1 The Bad Breath Paradox

Among the 1245 individuals seen in the Rio de Janeiro halitosis clinic (1199 in this specific analysis), those who stated that they perceived their own bad breath tended to show objectively less intense bad breath than those who stated that they did not perceive their own bad breath. The individuals who stated that they perceived their own bad breath showed lower Halimeter™ scores than those individuals who had their bad breath identified by a close person rather than by themselves. The highest Halimeter™ scores were found among individuals that a close person perceived, but they did not perceive themselves their bad breath (Table 14.4).

The data presented here and also from most studies elsewhere are based on samples of patients who sought care due to concerns with bad breath. These are clearly special populations. There should be studies that investigate these issues in general populations of non-patients, in order to obtain conclusive information about the methods of diagnosis-detection of bad breath in general. Information about reproducibility of the assessments was not presented here, though this is probably the most relevant aspect to ensure the accuracy of bad breath detection methods.

As indicated, self-assessment seems to be an invalid method of bad breath detection [19]. Close persons seem to be more reliable assessors, and VSC seems to measure only partially what we want. Apparently, the information given directly by a close person to the health professional and the organoleptic assessment by a trained professional who smells the individual's breath are the most reliable (accurate) methods for the detection of bad breath [10].

For epidemiological studies a good alternative is to interview family members as informants [20]. "A recent Brazilian study of the prevalence of oral malodour assessed its presence by surveying university students (as "informants") regarding the prevalence of persisting malodour in members of their households. This was an interesting methodology as it overcomes the limitations of self-reporting of malodour whilst retaining the subjective judgment of malodour; the design might also facilitate the recruitment of large numbers of subjects." [3]. There are other advantages of the method used in that study: it reflected real life detection of objectionable odor by common people, not by an expert; it detected people who present malodor constantly, not only at a one-off examination in a research setting; and although there usually is a consensus in social circles about who does and does not have oral malodor [21], using only one or two assessors might not reflect this social consensus. Using a large number of assessors was a way of obtaining information, which would, more likely, reflect a social consensus regarding the presence of bad breath; people might feel embarrassed to report that an individual presents bad breath in front of that individual, which may underestimate the presence of bad breath. In that study, the informant reported about the problem directly to the researcher confidentially and independently from the presence and knowledge of the individual who suffered from bad breath [20].

Table 14.4 Halimeter™ scores according to self-perception of breath and information by a close person

Perception of bad breath (*n*)	Halimeter™ scores (mean)
Self **no** and close person **no** (82)	97 ppb
Self **yes** and close person **no** (288)	98 ppb
Self **no** and close person **yes** (465)	200 ppb
Self **yes** and close person **yes** (364)	150 ppb

14.3 Prevalence of Bad Breath

Some studies, in different ways, investigated the prevalence of bad breath [20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. As explained, one of the main challenges for the study of bad breath is the difficulty in measuring it. People who have bad breath often are not aware of it, while others who are certain that they have it in reality do not have it. Preconceived notions confound the self-assessment of breath odor [1]. For that reason, simply asking the person whether she has bad breath is of limited validity. A relatively more valid way is to ask the person whether someone close to her reported recently that she has bad breath. Even this strategy is vulnerable

to information bias, as many people, despite being a close relative or friend, do not alert the sufferer with the fear of hurting the person's feelings. Even in modern societies, bad breath carries a social stigma, maybe related to repulsive feelings towards dirt and disease. Thus, this strategy may underestimate the real prevalence of bad breath. The independent direct reporting of a close person to the professional researcher reduces the risk of this bias [10, 20].

Table 14.5 summarizes the results of the studies that investigated the prevalence of bad breath. The prevalence varied from 15% to 58%. These values are not comparable as the studies used different methods for the measurement detection of bad breath and the type of study population.

Table 14.5 Prevalence of bad breath

Country	Prevalence (%)	Method of measuring-detecting bad breath
USA – study 1	24	Information from a close person (indirectly)
USA – study 2	31	Self-assessment
Korea – study 1	58	Self-assessment
Korea – study 2	24	Self-assessment
Japan – study 1	19	Self-assessment
Japan – study 2	32	VSC > 75 ppb[a]
Japan – study 3	24	VSC > 96 ppb
Japan – study 4	8, 15, 18, 25[b]	VSC > 75 ppb
Brazil – study 1	15	Information from a close person (directly)
Brazil – study 2	42	VSC > 90 ppb
China	27	Trained professional smelling the individual's breath
Italy	54	Trained professional smelling the individual's breath
Switzerland	11	Trained professional smelling the individual's breath

Sources: Miyazaki et al. [30], Loesche et al. [27], Miyazaki et al. [29], Meskin [28], Yeagaki et al. [33], Lee et al. [25], Sato et al. [31], Personal communication with Ana Cristina Kolbe, Liu et al. [26], Nadanovsky et al. [20], Bornstein et al. [23], Aimetti et al. [22], Kim et al. [24]

[a]*VSC* volatile sulfur compounds concentration assessment

[b]Percentages refer to measurements taken in early afternoon, early morning, late afternoon, and late morning, respectively

The most frequent problems of the studies that investigated the prevalence of bad breath are the way the participants were selected, the response rate, and the way of measuring-detecting bad breath. In general, studies did not report how participants were selected. In some studies participants were voluntaries without a clear definition of the study population. If we are to trust prevalence data, it is necessary that each eligible person in the study population had the same chance of being included. Response rates were rarely reported. All of these limitations suggest a high risk of bias. In fact, epidemiological studies usually find marked demographic and health differences between participants and non-participants. In addition, most studies did not report any measure of precision of the estimates, such as confidence interval.

In summary, we do not know, with confidence, the prevalence of bad breath. The best available information is that approximately 15% (95%CI 11–19) of the population present bad breath constantly, according to the information given directly to the researcher by a close person who lives in the same household as the individual in focus [20]. There is a need of studies in different populations to confirm or widen this information.

14.4 Causes of Bad Breath

14.4.1 Mechanisms of Bad Breath Formation

Malodorous gases, mainly volatile sulfur compounds (VSC), are formed from the metabolism of bacteria in the mouth. The proliferation of these bacteria is stimulated by proteins, mainly epithelial cells from the mouth mucosa. These bacteria transform proteins into amino acids, some of which contain sulfur and are the precursors of VSC. It appears that the main VSC that cause bad breath are hydrogen sulfide (H2S) and methyl mercaptan (CH3SH) [15, 34]. Other volatile compounds, not sulfur, also contribute to bad breath, such as Skatole [35].

Saliva plays a key role in the mechanism of bad breath formation. It is a source of oxygen, which avoids bad breath. On the other hand, saliva contains substances that favor bad breath such as peptides and proteins. A fast or intense salivary flux and greater availability of oxygen and therefore fewer opportunities for the degradation of peptides and proteins may result in the predominance of the properties of saliva that inhibit bad breath. On the other hand, when conditions are reversed, such as during sleep, in which the salivary

flux and availability of oxygen are lower, bad breath provoked by saliva is favored. This is why bad breath is worse after waking up in the morning. Saliva influences the acid-base mechanism of bacteria, and it determines the pH. The pH plays a central role in bad breath formation. An acid pH reduces or inhibits bad breath, while a pH close to neutrality and alkaline favors it [36]. A higher quantity of cadaverine in saliva also contributes to bad breath [37], and more immunoglobulin A (IgA) reduces the quantity of bacteria on the tongue's torso [38, 39].

Individually, bad breath during the day is inversely associated with salivary flux; when it is slower, for example, during sleep or fasting, bad breath increases. On the other hand, chewing increases salivary flux with a concomitant increase in the cleaning of the oral mucosa and reduction in bad breath. Curiously, despite this common observation, clinical studies did not find an association between salivary flux and bad breath. Moreover, xerostomic patients do not seem to present higher prevalence of bad breath. A plausible explanation is that bad breath occurs mainly in an alkaline micro environment, while saliva is often acid in people with xerostomia [40, 41].

Factors that are responsible for the reduction of the salivary flux, and therefore for the increase in bad breath, are the following: longtime fasting, sleep, emotional stress, increase in age, exercise, talking continuously, some medications, Sjogren syndrome, chemotherapy, rheumatoid arthritis, radiotherapy, and diabetes.

Bad breath may be caused by systemic problems that have other mechanisms, but they are infrequent. Hydrogen sulfide (H2S) and methyl mercaptan (CH3SH) are related to bad breath of non-systemic origin, mainly through the metabolism of some oral bacteria and nasal, bronchial, and pulmonary infections. Bad breath of systemic origin is related to dimethyl sulfide (CH3SCH3). CH3SCH3 is transported from other parts of the body, for example, from the liver in cases of liver cirrhosis, by the blood until it reaches the air in the lung and exits through the air exhaled from the mouth and nose [42].

14.4.2 Tongue Coating (Debris, Bacteria, and Dead Cells)

The main site in the mouth where VSC are produced is on the upper surface of the tongue, where a proteolytic bacteria flora reside [12, 43, 44]. The bigger the quantity of IgA in saliva, the smaller the quantity of this tongue coating is [39], and the bigger the quantity of bacteria on the tongue upper surface, the higher the VSC concentration is in the mouth air and the risk of bad breath [29, 30, 44–46].

14.4.3 Periodontal Disease

Periodontal disease is associated with bad breath [47], be it due to a direct causal mechanism or to an independent factor affecting both conditions. There is also the possibility that the VSC cause periodontal disease [48]. May be all of these mechanisms occur simultaneously [49, 50, 51]. Most probably some causes of periodontal disease are also causes of bad breath. It was possible to eliminate bad breath without eliminating periodontal disease [45], and periodontal therapy was capable of reducing bad breath in patients with periodontal disease and bad breath [52].

► Box 14.2 lists the main causes of bad breath of oral origin. Tongue coating and periodontal disease were investigated in clinical and laboratorial research, while oral hygiene and debris were implicated through clinical observations [10].

Box 14.2 The main causes of bad breath of oral origin

Tongue coating
Periodontal pocket
Gingival bleeding
Poor oral hygiene
Debris under restorations

14.4.4 Airways

The larynx, the pharynx, the throat, the nose, the sinuses, and the lungs can be associated with bad breath. Many ear, nose, and throat (ENT) doctors believe that problems in these regions are frequent causes of bad breath, especially the upper airways ([53], 54, 55]). The impairment of the function of the lung due to pulmonary abscess, foreign body, necrotizing pneumonia, cancer, or tuberculosis is rare but may cause bad breath. The main airways factors that are often involved in the cause of bad breath are listed in ► Box 14.3. There is insufficient evidence implicating the tonsils [56].

Box 14.3 The main airways factors that are often involved in the cause of bad breath

Postnasal drip
Chronic sinusitis
Infected tonsils
Foreign body in the nose

14.4.5 Transitory Bad Breath

This type of bad breath originates in odorous substances that are excreted from the blood via the lung. After entering the blood through digestion, the skin or the airways, these substances are exhaled by the lung air, the skin, etc. This type of bad breath may last for hours (► Box 14.4). The following are examples of this mechanism [57]: the smell of alcohol, garlic, acetone, or rotting fruit in untreated diabetes; the smell of urea (ammonia) in kidney dysfunction; and the smell of blood in liver dysfunction (cirrhosis). There may be an increase in VSC that lasts 1–3 days after the end of the menstruation [58]. It appears that not only VSC increases in the pre and menstrual phases, but the salivary flux reduces in these phases in comparison to the follicular phase and to men. In addition, salivary cortisol appears to increase during the menstrual phase [59]. Some medications cause transitory bad breath [60].

Box 14.4 Causes of transitory bad breath
Fasting
Garlic, onion, and pepper
Alcohol
Smoking
Coffee
Some medications (nitrate, hydrate chlorine, iodine)
Menstruation

14.4.6 Systemic Diseases

As in the transitory type, halitosis originating in systemic diseases occurs due to odorous substances that are exhaled from the lung: volatile products of these diseases are metabolized in the blood and captured by the lung, from where they are expelled by the exhaled air. One example of this type of halitosis is trimethylaminuria, an inherited digestive enzyme deficiency that may cause a fishy smell in the urine and in the breath [61] (► Box 14.5).

Box 14.5 Systemic diseases that cause bad breath
Liver diseases (cirrhosis, liver failure)
Kidney failure
Diabetes
Allergies
Trimethylaminuria

14.4.7 Gastrointestinal Diseases

Contrary to common belief, it seems that bad breath of gastrointestinal origin is very rare. In any case, many gastroenterologists believe that some gastric problems are frequent causes of bad breath. Few studies investigated whether gastric problems are in fact causes of halitosis [10, 62–64]. There is suspicion that occasionally disease in the upper gastrointestinal tract may cause halitosis [4]. The main suspects are the following: inadequate closure of the esophagus (reflux, pyloric stenosis, hiatus hernia); malabsorption syndrome; gastric carcinoma; ulcers; *Helicobacter pylori*; and Crohn's disease.

14.5 Treatment of Bad Breath

The usual procedures are listed in Box 14.6. Depending on the main causes in each particular patient, usually two or three procedures are selected from this list [12, 65, 66].

Nadanovsky and Britto [67] published a small book, with a preface by Mel Rosenberg (available in print and electronic versions – only in Portuguese – ► http://www.e-papers.com.br/ or ► http://www.e-papers.com.br/produtos.asp?codigo_produto=1036&promo=0), detailing a step-by-step explanation with a flowchart of the treatment of halitosis. This book can be used by lay people as a self-help guide and by dentists when treating patients with halitosis in their clinic. Also, a group of experts published an international consensus for the treatment of halitosis in the dental clinic [68].

Box 14.6 The usual procedures in the treatment of bad breath. Two or three procedures are often selected from this list
Psychological management
Antibacterial local chemical products (toothpaste, mouth rinse)
Antibacterial systemic products (antibiotics)
Oral hygiene instructions
Professional mechanical cleaning of the mouth
Salivary stimulants or substitutes (artificial saliva)
Control of postnasal drip
Avoidance of odorous foods and medications
Correction of anatomic anomalies
Medical management of systemic diseases

It is very important to pay special attention to the psychological aspects and be sensitive to the patient. It is

key for the success of halitosis treatment to ask and say the right things at the right moments [69]. Many people who are concerned with bad breath and seek treatment in fact do not have bad breath, in our clinical experience, approximately 30%. These patients present distinct psychological profiles. Each psychological profile demands a different approach [16, 70–73]. For example, it is necessary to be extra careful with the "*halitophobic*" patients, i.e., those that suffer from imaginary halitosis, pseudohalitosis, or halitophobia [74], approximately 7% in our experience. In these patients the concern with bad breath may function as a "social crutch" to justify some difficulties in social relationships. The health professional should not remove the crutch abruptly as this might cause a psychological impact difficult to be overcome. The halitophobic patient tends to react with hostility and incredulity towards the person who informs him that there is no bad breath. Though unlikely, there is also the possibility that the patient in fact is able to smell his own bad breath that no one else is able to perceive, as it may dissipates in the air before reaching another person's nose. Some people may have suffered from bad breath in the past, solved the problem, but are still under the impression that the problem persists. Others equate a bitter taste with bad breath, though these two conditions are not related. Psychological management demands excellent communication skills by the professional; this is one of the most valuable skills for the success of bad breath treatment. Unfortunately there seems to be too much unnecessary and inadequate treatment provided by doctors and dentists to patients whose main complaint is bad breath [75]. This is an area still much needy of research.

The prescription of antibacterial local chemical products (via toothpaste and mouth rinse) appears to be effective. Professionals ought to be up to date because there is a plethora of mouth rinse and toothpaste options available in the market, and only some of them seem to have a tangible benefit to the breath odor [76, 77, 78, 79, 80, 81, 82, 83]. Randomized controlled trials (RCT) testing products specifically for bad breath have been carried out, and formulations with the best evidence of benefit and fewer adverse effects should be chosen [84, 85]. However, there is a lack of RCT with large number of participants and long periods of intervention and follow-up [7]. The chemical control of caries through fluoride toothpaste has been arguably the main reason for improvements in oral health. Toothpastes with substances that inhibit the formation of bacterial plaque and calculus have also been shown to be effective and may have been important for the improvements in periodontal health. Bad breath could also benefit from this kind of local chemical control. Some of the agents that seem to be effective are listed in ► Box 14.7.

Box 14.7 Local antibacterial chemical agents that seem to be effective to prevent and treat bad breath. These are usually delivered via toothpastes and mouth rinses

Cetylpyridinium chloride
Chlorhexidine
Triclosan
Oxidizing agents, such as chlorine dioxide
Essential oils
Zinc salts
Two-phase oil-water mouthwashes

Systemic antibiotics are prescribed only in a few cases of bad breath associated with severe chronic periodontal disease, or severe infection of the tonsils, sinuses, or throat. In our experience, these comprise approximately 5% of patients who seek care due to bad breath.

One of the main aspects of bad breath treatment is the cleaning of the mouth, especially the local mechanical cleaning of the tongue dorsum [86]. This can be performed with the toothbrush, but it appears to be easier and more effective when tongue cleaners are used [87, 88]. However, there is a lack of RCT about the effectiveness of tongue cleaning in the prevention and treatment of bad breath, either with the toothbrush or with the tongue cleaner [8, 9]. Professional tooth cleaning helps reduce bad breath in patients with periodontitis [89]. In our experience, only a few patients needed professional tooth cleaning in order to help and solve their bad breath problem. Some patients benefited from careful instructions regarding personal oral hygiene (► Box 14.8).

Box 14.8 Local mechanical cleaning: personal oral hygiene careful instructions and professional cleaning

Tongue cleaning
Tooth brushing
Inter-dental cleaning
Denture cleaning
Professional sub-gingival cleaning

Some patients present a reduced salivary function. In these cases, it may be useful to try salivary stimulants or substitutes (► Box 14.9). Pilocarpine may be prescribed in the most severe cases of xerostomia, as patients with Sjogren syndrome or under radiotherapy of the head or neck. It stimulates the production of saliva in persons with reduced salivary flux but with remaining viable salivary glands. The adverse effects of pilocarpine are nausea, vomit, dizziness, diarrhea, feeling that the blad-

der is full, sweating, and bradycardia (a reduction in heart beats). Chewing gums with some active ingredients, such as probiotics lactobacillus, zinc acetate and magnolia bark extract, eucalyptus-extract, and allyl isothiocyanate (AITC) with zinc lactate, may help reduce halitosis [90].

Box 14.9 Alternatives to stimulate salivary flux or to replace saliva

Drink water several times during the day
Non-sugar chewing gum
Eat something several times during the day
Saliva substitute (artificial saliva)
Pilocarpine

Postnasal drip is implicated in bad breath of many patients. When the control of the postnasal drip is attempted, it should be supervised by an ENT specialist or a doctor specialized on allergies. They may prescribe corticosteroid nasal spray for the control of mucus and rhinitis, vaccines for desensitization, and allergenic control through air filters, non-allergic products and room humidifiers.

Some foods and medications cause transitory halitosis. As the metabolic digestive process lasts from 1 to 5 hours, depending on the quantity and type of food, drink, or medication consumed, it is possible to mask the bad smell with constant mouth rinses, mint tablets, and other palliative alternatives.

Some anatomic deviations may need to be corrected in order to treat bad breath in specific patients, but these situations are rare in our clinical experience. Some examples are the following: surgical removal of periodontal pockets; repair of grossly defective dental restorations or prostheses; removal of foreign body from the nose, sinus, or lungs; and removal of cracks that retain foods in the tonsils or pharynx.

When there is suspicion or confirmed systemic or gastric disease that could be the cause of the bad breath, the patient should be referred to a general practitioner or a specialist doctor.

14.6 The Experience of a Halitosis Clinic in Rio de Janeiro from 1998 to 2004 ("Clínica do Tratamento do Hálito – CTH-RJ")

Using several ways of advertising such as newspaper, television, radio, and the Internet, a clinic dedicated exclusively to the treatment of bad breath (CTH-RJ) recruited 1245 patients between 1998 and 2004. Of these, one-third was informed that they did not have chronic halitosis, and therefore no treatment was prescribed. In this group it is included people with imaginary halitosis, pseudohalitosis, or halitophobia, who comprised 7% of the 1245 patients assessed. The other two-thirds initiated treatment, but only 434, i.e., approximately one-third, completed it. The results of the treatment reported from now onwards refer to these patients who needed and returned to complete the treatment (Fig. 14.1).

Before treatment, the VSC concentration in the mouth air, measured by the Halimeter™, had a mean of 200 ppb. After treatment this concentration reduced to a mean of 50 ppb. In addition, before treatment 88% of the patients were classified as having very bad, bad, or moderate odor in the five points organoleptic scale, while after treatment none had very bad or bad, and only 3% had moderate odor (Table 14.6). Those 13% classified as having very good or good odor before treatment were treated because they presented obvious risk factors and VSC concentrations above 200 ppb.

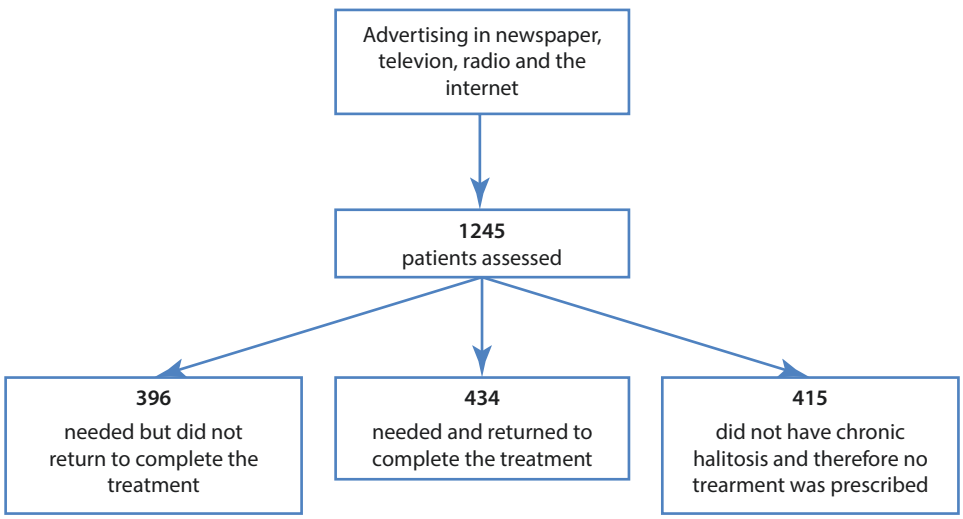


Fig. 14.1 Flowchart of the patients who sought treatment in the halitosis clinic in Rio de Janeiro from 1998 to 2004 ("Clínica do Tratamento do Hálito – CTH-RJ")

Table 14.6 Organoleptic classification of the breath odor among patients who presented chronic halitosis and completed treatment in the CTH-RJ, before and after treatment

Organoleptic classification of breath odor before and after treatment				
	Before		After	
	n	%	*n*	%
Very bad odor	38	9	0	0
Bad odor	211	49	1	0
Moderate odor	128	29	12	3
Good odor	37	9	119	28
Very good odor	19	4	298	69
Total	433	100	430	100

Several procedures, prescriptions, and recommendations were applied during the course of the halitosis treatment of these patients. The selection of the specific ones according to each patient was based on the risk factors presented by each patient, the type and the frequency and intensity of the bad breath. Some recommendations, such as tongue cleaning and toothpaste specific for the control of bad breath, were made to all patients. Many patients needed, in addition, other procedures that are listed in ▶ Box 14.10. Two or three visits in a period of 2 months were the most common schedule (Table 14.7).

Table 14.7 Number of visits during treatment courses of the 434 patients who presented chronic halitosis and completed treatment in the CTH-RJ (a halitosis clinic in Rio de Janeiro, Brazil) between 1998 and 2004

Number of visits	Number of patients
2	181 (42%)
3	205 (47%)
4	39 (9%)
5, 6, or 7	8 (2%)
11	1 (0%)
Total	434 (100%)

Box 14.10 Treatment provided to the 434 patients who presented chronic halitosis and completed treatment in the CTH-RJ (a halitosis clinic in Rio de Janeiro, Brazil) between 1998 and 2004. Usually two or three items of this list were selected, depending on the risk factors presented by each patient, the type and the frequency and intensity of the bad breath

Tongue cleaning instruction
Drink water several times in the day
Eat something every 2 or 3 hours
Tooth brushing instruction
Inter-dental cleaning instruction
Sugarless chewing gum
Umeboshi plum
Artificial saliva
Pilocarpine
Metronidazole
Tetracycline
Chlorhexidine
Triclosan
Chlorine dioxide
Listerine
Zinc chloride
Cetylpyridinium chloride
Referred to the following treatments (sporadically): grossly defective dental restoration; periodontal treatment; ENT doctor; gastroenterologist; and general medical practitioner

The treatment provided at the CTH-RJ appears to be very effective, but this research was not an RCT. Our evaluation was limited to a before-after comparison without a control group. Also, patients were assessed immediately after the end of the treatment course. There is a clear need for RCT that assess patients at least 12 or 24 months after treatment in order to find out whether the control of bad breath is in fact effective and sustainable for a reasonable period of time.

14.7 Conclusion

Most adults present occasional bad breath, mainly when they wake up or when they remain for long hours without eating, while 15% have bad breath constantly. People

are unreliable assessors of their own bad breath; those who stated that they perceived their own bad breath tended to show objectively less intense bad breath than those who stated that they did not perceive their own bad breath. A close family member acting as an "informant" is the best way to detect persisting bad breath. The vast majority of cases of bad breath are caused by oral bacteria. Treatment appears to be very effective in the short term. However, the evidence is mostly based not on randomized controlled trials, and the certainty of the available evidence is weak due to important methodological limitations, that is, high risk of biases. There is a clear need for randomized controlled trials that assess patients at least 12 or 24 months after treatment in order to find out whether the control of bad breath is in fact effective and sustainable for a reasonable period of time.

Points of Emphasis

- The information given directly by a close person and the organoleptic assessment by a trained professional who smells the individual's breath are the best methods for the detection of bad breath. Self-assessment is an invalid method of bad breath detection.
- The best available information is that approximately 15% (95%CI 11–19) of the population present persisting bad breath.
- The main causes of bad breath are malodorous gases, mainly volatile sulfur compounds that are formed from the metabolism of bacteria in the mouth.
- Many people who are concerned with bad breath and seek treatment in fact do not have bad breath, in our halitosis clinic, approximately 30%.
- The treatment provided in our halitosis clinic appears to be very effective, but this research was not a randomized controlled trial (RCT). Our evaluation was limited to a before-after comparison without a control group, no blinding, and too many patients were lost in the follow-up. Also, patients were assessed immediately after the end of the course of treatment. There is a clear need for RCTs that assess patients at least 12 or 24 months after treatment in order to find out whether the control of bad breath is in fact effective and sustainable for a reasonable period of time.

References

1. Rosenberg M. The science of bad breath. Sci Am. 2002;286(4):72–9.
2. Fukui M, Hinode D, Yokoyama M, Yoshioka M, Kataoka K, Ito H. Levels of salivary stress markers in patients with anxiety about halitosis. Arch Oral Biol. 2010;55:842–7.
3. Hughes FJ, McNab R. Oral malodour – a review. Arch Oral Biol. 2008;53(Suppl 1):S1–7.
4. Porter SR. Diet and halitosis. Curr Opin Clin Nutr Metab Care. 2011;14:463–8.
5. Rösing CK, Loesche W. Halitosis: an overview of epidemiology, etiology and clinical management. Braz Oral Res. 2011;25:466–71.
6. Scully C, Greenman J. Halitology (breath odour: aetiopathogenesis and management). Oral Dis. 2012;18:333–45.
7. Fedorowicz Z, Aljufairi H, Nasser M, Outhouse TL, Pedrazzi V. Mouth rinses for the treatment of halitosis. Cochrane Database Syst Rev. 2008;(4):CD006701.
8. Outhouse TL, Al-Alawi R, Fedorowicz Z, Keenan JV. Tongue scraping for treating halitosis. Cochrane Database Syst Rev. 2006;(2):CD005519.
9. Van der Sleen MI, Slot DE, Van Trijffel E, Winkel EG, Van der Weijden GA. Effectiveness of mechanical tongue cleaning on breath odour and tongue coating: a systematic review. Int J Dent Hygiene. 2010;8:258–68.
10. Nadanovsky P. Evidência científica sobre prevalência, diagnóstico e causas da halitose. In: Rosenberg M, editor. Halitose: perspectivas em Pesquisa. 2a ed. Rio de Janeiro: Guanabara Koogan; 2003. p. 135–56.
11. Greenman J, Duffield J, Spencer P, Rosenberg M, Corry D, Saad S, Lenton P, Majerus G, Nachnani S, El-Maaytah M. Study on the organoleptic intensity scale for measuring Oral malodor. J Dent Res. 2004;83:81–5.
12. Loesche WJ, Kazor C. Microbiology and treatment of halitosis. Periodontology. 2002;2000(28):256–79.
13. Nadanovsky P, Nadanovsky AN, Britto SH. VSC, organoleptic assessment, self and third party assessed breath odour. In: Brunette D, Newman M, et al., editors. Proceedings of the fourth international conference on breath odor, Aug 20–21, 1999. Los Angeles: International Society for Breath Odor Research and the UCLA Center for the Health Sciences; 1999.
14. Kim DJ, Lee JY, Kho HS, Chung JW, Park HK, Kim YK. A new organoleptic testing method for evaluating halitosis. J Periodontol. 2009;80:93–7.
15. Van den Velde S, van Steenberghe D, Van Hee P, Quirynen M. Detection of odorous compounds in breath. J Dent Res. 2009;88:285–9.
16. Oho T, Yoshida Y, Shimazaki Y, Yamashita Y, Koga T. Characteristics of patients complaining of halitosis and the usefulness of gas chromatography for diagnosing halitosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001a;91:531–4.
17. Tanaka M, Anguri H, Nonaka A, Kataoka K, Nagata H, Kita J, Shizukuishi S. Clinical assessment of oral malodor by the electronic nose system. J Dent Res. 2004;83:317–21.

18. Nakhleh MK, Quatredeniers M, Haick H. Detection of halitosis in breath: between the past, present, and future. Oral Dis. 2018;24:685–95.
19. Bornstein MM, Stocker BL, Seemann R, Bürgin WB, Lussi A. Prevalence of halitosis in young male adults: a study in Swiss army recruits comparing self-reported and clinical data. J Periodontol. 2009a;80:24–31.
20. Nadanovsky P, Carvalho LBM, Ponce de Leon A. Oral malodour and its association with age and sex in a general population in Brazil. Oral Dis. 2007;13:105–9.
21. Rosenberg M, McCulloch CA. Measurement of oral malodor: current methods and future prospects. J Periodontol. 1992;63:776–82.
22. Aimetti M, Perotto S, Castiglione A, Ercoli E, Romano F. Prevalence estimation of halitosis and its association with oral health-related parameters in an adult population of a city in North Italy. J Clin Periodontol. 2015;42:1105–14.
23. Bornstein MM, Kislig K, Hoti BB, Seemann R, Lussi A. Prevalence of halitosis in the population of the city of Bern, Switzerland: a study comparing self-reported and clinical data. Eur J Oral Sci. 2009b;117:261–7.
24. Kim SY, Sim S, Kim S-G, Park B, Choi HG. Prevalence and associated factors of subjective halitosis in Korean adolescents. PLoS One. 2015;10(10):e0140214.
25. Lee SW, Kim HS, Park MS. Epidemiology of oral malodor in Koreans. In: Brunette D, Newman M, et al., editors. Proceedings of the fourth international conference on breath odor, Aug 20–21, 1999. CA. International Society for Breath Odor Research and the UCLA Center for the Health Sciences: Los Angeles; 1999. p. 33.
26. Liu XN, Shinada K, Chen XC, Zhang BX, Yaegaki K, Kawaguchi Y. Oral malodorrelated parameters in the Chinese general population. J Clin Periodontol. 2006;33:31–6.
27. Loesche WJ, Grossman N, Dominguez L, Schork MA. Oral malodour in the elderly. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 165–79.
28. Meskin LH. A breath of fresh air [editorial]. J Am Dent Assoc. 1996;127:1282, 1284, 1286.
29. Miyazaki H, Fujita C, Soh I, Tekahara T. Relationship between volatile sulphur compounds and oral conditions in the general Japanese population. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 165–79.
30. Miyazaki H, Sakao S, Katoh Y, Takehara T. Correlation between volatile sulphur compounds and certain oral health measurements in the general population. J Periodontol. 1995;66:679–84.
31. Sato N, Yamazaki M, Matsuda H, et al. Investigation of consciousness for foul breath in Japanese. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. Tokyo: International Society for Breath Odor Research and the National Center of Science; 2001. p. 43.
32. Silva M, Leite FRM, Ferreira LB, Pola NM, Scannapieco FA, Demarco FF, Nascimento GG. Estimated prevalence of halitosis: a systematic review and meta-regression analysis. Clin Oral Invest. 2018;22:47–55.
33. Yeagaki K, Matudaira H, Sano S, Kitamura T. Attitudes towards one's and other's oral malodour. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 217–30.
34. Awano S, Koshimune S, Kurihara E, Gohara K, Sakai A, Soh I, Hamasaki T, Ansai T, Takehara T. The assessment of methyl mercaptan, an important clinical marker for the diagnosis of oral malodor. J Dent. 2004;32:555–9.
35. Kleinberg I, Codipilly DPM, Globerman DY. Oxygen depletion by oral microbiota and its role in oral malodour formation. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 95–109.
36. Kleinberg I, Westbay G. Salivary and metabolic factors involved in oral malodor formation. J Periodontol. 1992;63:768–75.
37. Goldberg S, Kozlovsky A, Gordon D, Gelernter I, Sintov A, Rosenberg M. Cadaverine as a putative component of oral malodor. J Dent Res. 1994;73:1168–72.
38. Fukui M, Matsuoka N, Akagi T, et al. The relationship between tongue plaque and secretory-IgA in saliva from patients with breath odor. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. International Society for Breath Odor Research and the National Center of Science: Tokyo; 2001. p. 67.
39. Hinode D, Fukui M, Yokoyama N, Yokoyama M, Yoshioka M, Nakamura R. Relationship between tongue coating and secretory-immunoglobulin A level in saliva obtained from patients complaining of oral malodor. J Clin Periodontol. 2003;30:1017–23.
40. Kleinberg I, Wolff MS, Codipilly DM. Role of saliva in oral dryness, oral feel and oral malodour. Int Dent J. 2002;52(Suppl 3):236–40.
41. Koshimune S, Awano S, Gohara K, Kurihara E, Ansai T, Takehara T. Low salivary flow and volatile sulfur compounds in mouth air. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96:38–41.
42. Tangerman A, Jansen JBMJ. Differentiation between local oral halitosis and extra-oral systemic halitosis – examples of halitosis of metabolic origin. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. Tokyo: International Society for Breath Odor Research and the National Center of Science; 2001. p. 35.
43. de Boever E, Uzeda M, Loesche WJ. Relationship between volatile sulfur compounds, BANA-hydrolyzing bacteria and gingival health in patients with and without complaints of oral malodor. J Clin Dent. 1994;4:114–9.
44. de Boever E, Loesche WJ. Assessing the contribution of anaerobic microflora of the tongue to oral malodor. J Am Dent Assoc. 1995;126:1384–93.
45. Bosy A, Kulkarni GV, Rosenberg M, McCulloch CA. Relationship of oral malodor to periodontitis: evidence of independence in discrete subpopulations. J Periodontol. 1994;65:37–46.
46. Rahardjo A, Miyazaki H. Oral malodor survey of Tebet community in Jakarta, Indonesia. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. Tokyo: International Society for Breath Odor Research and the National Center of Science; 2001. p. 63.
47. Silva M, Cademartori MG, Leite FRM, López R, Demarco FF, Nascimento GG. Is periodontitis associated with halitosis? A systematic review and meta-regression analysis. J Clin Periodontol. 2017;44:1003–9.
48. Ratkay LG, Tonzetich J, Waterfield JD. The effect of methyl mercaptan on the enzymatic and immunological activity leading to periodontal tissue destruction. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 35–46.
49. Figueiredo LC, Rosetti EP, Marcantonio E Jr, Marcantonio RA, Salvador SL. The relationship of oral malodor in patients with or without periodontal disease. J Periodontol. 2002;73:1338–42.
50. Lee CH, Kho HS, Chung SC, Lee SW, Kim YK. The relationship between volatile sulfur compounds and major halitosis-inducing factors. J Periodontol. 2003;74:32–7.

51. Morita M, Wang H-L. Association between oral malodor and adult periodontitis: a review. J Clin Periodontol. 2001;28:813–9.
52. Takeuchi H, Machigashira M, Yamashita D, Kozono S, Nakajima Y, Miyamoto M, Takeuchi N, Setoguchi T, Noguchi K. The association of periodontal disease with oral malodour in a Japanese population. Oral Dis. 2010;16:702–6.
53. Bollen CM, Rompen EH, Demanez JP. Halitosis: a multidisciplinary problem. Rev Med Liege. 1999;54:32–6.
54. Finkelstein Y, Talmi YP, Zohar Y, Ophir D. Endoscopic diagnosis and treatment of persistent halitosis after pharyngeal flap surgery. Plast Reconstr Surg. 1993;92:1176–8.
55. Finkelstein Y, Talmi YP, Ophir D, Berger G. Laser cryptolysis for the treatment of halitosis. Otolaryngol Head Neck Surg. 2004;131:372–7.
56. Ferguson M, Aydin M, Mickel J. Halitosis and the tonsils: a review of management. Otolaryngol Head Neck Surg. 2014;151:567–74.
57. Massler M, Emsile RD, Bolden TE. Fetor ex ore – a review. Oral Surg Oral Med Oral Pathol. 1951;4:110.
58. Tonzetich J, Preti G, Huggins GR. Changes in concentration of volatile sulphur compounds of mouth air during de menstrual cycle. J Int Med Res. 1978;6:245–54.
59. Calil CM, Lima PO, Bernardes CF, Groppo FC, Bado F e Marcondes FK. Influence of gender and menstrual cycle on volatile sulphur compounds production. Arch Oral Biol. 2008;53:1107–12.
60. Torsten M, Gómez-Moreno G, Aguilar-Salvatierra A. Drug-related oral malodour (halitosis): a literature review. Eur Rev Med Pharmacol Sci. 2017;21:4930–4.
61. Mitchell SC. Trimethylaminuria (fish-odour syndrome) and oral malodour. Oral Dis. 2005;11(Suppl 1):10–3.
62. Hoshi K, Yamano Y, Mitsunaga A, Shimizu S, Kagawa J, Ogiuchi H. Gastrointestinal diseases and halitosis: association of gastric Helicobacter pylori infection. Int Dent J. 2002;52(Suppl 3):207–11.
63. Katz J, Shenkman A, Stavropoulos F, Melzer E. Oral signs and symptoms in relation to disease activity and site of involvement in patients with inflammatory bowel disease. Oral Dis. 2003;9:34–40.
64. Kislig K, Wilder-Smith CH, Bornstein MM, Lussi A, Seemann R. Halitosis and tongue coating in patients with erosive gastroesophageal reflux disease versus nonerosive gastroesophageal reflux disease. Clin Oral Invest. 2013;17:159–65.
65. Quirynen M, Zhao H, Steenberghe D. Review of the treatment strategies for oral malodour. Clin Oral Invest. 2002;6:1–10.
66. Yaegaki K, Coil JM, Kamemizu T, Miyazaki H. Tongue brushing and mouth rinsing as basic treatment measures for halitosis. Int Dent J. 2002;52(Suppl 3):192–6.
67. Nadanovsky P, Britto SH. Hálito: passo a passo para um hálito agradável. Rio de Janeiro: E-papers. 2007. http://www.e-papers.com.br/ or http://www.e-papers.com.br/produtos.asp?codigo_produto=1036&promo=0.
68. Seemann R, Conceicao MD, Filippi A, Greenman J, Lenton P, Nachnani S, Quirynen M, Roldan S, Schulze H, Sterer N, Tangerman A, Winkel EG, Yaegaki K, Rosenberg M. Halitosis management by the general dental practitioner-results of an international consensus workshop. J Breath Res. 2014;8:017101.
69. Lenton P, Majerus G, Bakdash B. Counseling and treating bad breath patients: a step-by-step approach. J Contemp Dent Pract. 2001;2:1–14.
70. Yaegaki K, Coil JM. Examination, classification, and treatment of halitosis-clinical perspectives. J Can Dent Assoc. 2000;66:257–61.
71. Oho T, Yoshida Y, Shimazaki Y, Yamashita Y, Koga T. Psychological condition of patients complaining of halitosis. J Dent. 2001b;29:31–3.
72. Murata T, Yamaga T, Iida T, Miyazaki H, Yaegaki K. Classification and examination of halitosis. Int Dent J. 2002;52(Suppl 3):181–6.
73. Coil JM, Yaegaki K, Matsuo T, Miyazaki H. Treatment needs (TN) and practical remedies for halitosis. Int Dent J. 2002;52(Suppl 3):187–91.
74. Suhas S, Sudarshan S, Pai KM. "Air bag" organoleptic behavioral experiment for managing fear of oral malodor. J Behav Ther Exp Psychiatry. 2004;35(1):13–5.
75. Seemann R, Bizhang M, Djamchidi C, Kage A, Nachnani S. The proportion of pseudo-halitosis patients in a multidisciplinary breath malodour consultation. Int Dent J. 2006;56:77–81.
76. Borden LC, Chaves ES, Bowman JP, Fath BM, Hollar GL. The effect of four mouth rinses on oral malodor. Compend Contin Educ Dent. 2002;23:531–6.
77. Niles HP, Vazquez J, Rustogi KN, Williams M, Gaffar A, Proskin HM. The clinical effectiveness of a dentifrice containing triclosan and a copolymer for providing long-term control of breath odor measured chromatographically. J Clin Dent. 1999;10:135–8.
78. Roldan S, Herrera D, Santa-Cruz I, O'Connor A, Gonzalez I, Sanz M. Comparative effects of different chlorhexidine mouthrinse formulations on volatile sulphur compounds and salivary bacterial counts. J Clin Periodontol. 2004;31:1128–34.
79. Rosing CK, Jonski G, Rölla G. Comparative analysis of some mouthrinses on the production of volatile sulfur-containing compounds. Acta Odontol Scand. 2002;60:10–2.
80. Sharma NC, Galustians HJ, Qaquish J, Galustians A, Rustogi KN, Petrone ME, Chaknis P, Garcia L, Volpe AR, Proskin HM. The clinical effectiveness of a dentifrice containing triclosan and a copolymer for controlling breath odor measured organoleptically twelve hours after toothbrushing. J Clin Dent. 1999;10:131–4.
81. Sreenivasan PK, Gittins E. Effects of low dose chlorhexidine mouthrinses on oral bacteria and salivary microflora including those producing hydrogen sulfide. Oral Microbiol Immunol. 2004;19:309–13.
82. Steenberghe D, Avontroodt P, Peeters W, Pauwels M, Coucke W, Lijnen A, Quirynen M. Effect of different mouthrinses on morning breath. J Periodontol. 2001;72:1183–91.
83. Young A, Jonski G, Rölla G. Inhibition of orally produced volatile sulfur compounds by zinc, chlorhexidine or cetylpyridinium chloride – effect of concentration. Eur J Oral Sci. 2003;111:400–4.
84. Ademovski SE, Mårtensson C, Persson GR, Renvert S. The long-term effect of a zinc acetate and chlorhexidine diacetate containing mouth rinse on intra-oral halitosis—a randomized clinical trial. J Clin Periodontol. 2017;44:1010–9.
85. Carvalho MD, Tabchoury CM, Cury JA, Toledo S, Nogueira-Filho GR. Impact of mouth rinses on morning bad breath in healthy subjects. J Clin Peridontol. 2004;31:85–90.
86. Quirynen M, Avontroodt P, Soers C, Zhao H, Pauwels M, van Steenberghe D. Impact of tongue cleansers on microbial load and taste. J Clin Periodontol. 2004;31:506–10.
87. Pedrazzi V, Sato S, Matos MGC, Lara EHG, Panzeri H. Tongue cleaning methods: a comparative clinical trial employing a toothbrush and a tongue scraper. J Periodontol. 2004;75:1009–12.
88. Seeman R, Kison A, Bizhang M, Zimmer S. Effectiveness of mechanical tongue cleaning on oral levels of volatile sulfur compounds. JADA. 2001;132:1263–7.
89. Deutscher HCD, Derman SHM, Barbe AG, Seemann R, Noack MJ. The effect of professional tooth cleaning or non-surgical periodontal therapy on oral halitosis in patients with periodontal diseases. A systematic review. Int J Dent Hygiene. 2018;16:36–47.
90. Muniz FWMG, Friedrich SA, Silveira CF, Rösing CK. The impact of chewing gum on halitosis parameters: a systematic review. J Breath Res. 2017;11:014001.

Recommended Readings

Amir E, Shimonov R, Rosenberg M. Halitosis in children. J Pediatr. 1999;134:338–43.

Anguri H, Tanaka M, Shizukuishi S. Clinical assessment of oral malodor with a new type of electronic nose. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. International Society for Breath Odor Research and the National Center of Science: Tokyo; 2001. p. 47.

Ben AH, Horowitz G, Nir D, Laufer D. Halitosis: an interdisciplinary approach. Am J Otolaryngol. 1998;19:8–11.

Brening RH, Sulser GF, Fosdick LS. The determination of halitosis by use of the osmoscope and the cryoscopy method. J Dent Res. 1939;18:127–32.

Coil JM, Tonzetich J. Characterization of volatile sulphur compounds production at individual gingival crevicular sites in human. J Clin Dent. 1992;3:97–103.

Crescenzo DG, Trastek VF, Allen MS, Deschamps C, Pairolero PC. Zenker's diverticulum in the elderly: is operation justified? Ann Thorac Surg. 1998;66:347–50.

Delanghe G, Ghyselen J, Feenstra L, van Steenberghe D. Experiences of a Belgian multidisciplinary breath odour clinic. Acta Otorhinolaryngol Belg. 1997a;51:43–8.

Delanghe G, Ghyselen J, van Steenberghe D, Feenstra L. Multidisciplinary breath-odour clinic [letter]. Lancet. 1997b;350(9072):187.

Evidence-Based Medicine Working Group. Evidence-based medicine – a new approach to teaching the practice of medicine. JAMA. 1992;268(17):2420–5.

Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. Philadelphia: Lippincott Williams & Wilkins; 1996.

Gerlach RW, Hyde JD, Poore CL, Stevens DP, Witt JJ. Breath effects of three marketed dentifrices: a comparative study evaluating single and cumulative use. J Clin Dent. 1998;9:83–8.

Grapp GL. Fetor oris (halitosis): a medical and dental responsibility. Northwest Med. 1933;32:375–80.

Greenstein RB, Goldberg S, Marku CS, Sterer N, Rosenberg M. Reduction of oral malodor by oxidizing lozenges. J Periodontol. 1997;68:1176–81.

Hirai M, Toya D, Tanaka N. Helicobacter pylori, a possible cause of oral malodor: a case report. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. International Society for Breath Odor Research and the National Center of Science: Tokyo; 2001. p. 51.

Hoshi K, Yamano Y, Matsuno H, et al. Possible association of gastric helicobacter pylori infection with oral odor. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. International Society for Breath Odor Research and the National Center of Science: Tokyo; 2001. p. 50.

Ierardi E, Amoruso A, La Notte T, Castellaneta S, Marrazza E, Monno RA, Francavilla A. Oral malodor (OM) and Helicobacter pylori (HP). Gut. 1997;41:A174.

Ierardi E, Amoruso A, La Notte T, Francavilla R, Castellaneta S, Marrazza E, Monno RA, Francavilla A. Halitosis and Helicobacter pylori: a possible relationship. Dig Dis Sci. 1998;43:2733–7.

Kleinberg I, Spielman A. Consensus report 3 – value of commercially available malodour meters. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 288–9.

Koriat H, Baht R, Eli I. Self-evaluation of oral malodor and its relation to physiologic measurements and body image characteristics. J Dent Res. 1999;78:545.

Kozlovsky A, Gordon D, Gelernter I, Loesche WJ, Rosenberg M. Correlation between the BANA test and oral malodor parameters. J Dent Res. 1994;73:1036–42.

Lee WC, Duignan MC, Walsh RM, McRae Moore JR. An audit of prophylactic antibiotic treatment following tonsillectomy in children. J Laryngol Otol. 1996;110:357–9.

Lee WC, Sharp JF. Complications of paediatric tonsillectomy postdischarge. J Laryngol Otol. 1996;110:136–40.

Lorber B. "Bad breath": presenting manifestation of anaerobic pulmonary infection. Am Rev Respir Dis. 1975;112:875–7.

Majerus GJ, Lenton PA, Hodges JS, et al. Methods of assessing oral malodor: variability, similarity and measurement levels. J Dent Res. 2001;80:715.

Morris PP, Read RR. Halitosis – variations in mouth and total breath odor intensity resulting from prophylaxis and antisepsis. J Dent Res. 1949;28:324–33.

Murata T, Fujiyama Y, Yamaga T, Miyazaki H. Breath malodor in an asthmatic patient caused by side-effects of medication: a case report and review of the literature. Oral Dis. 2003;9:273–6.

Nachnani S, Munoz B, Sunshine S, Hsiung C, Pierce K, Anson D. Electronic nose as a diagnostic tool in the detection of oral malodor. J Dent Res. 2000;79:445.

Nadanovsky P. Epidemiologia aplicada a clínica: um enfoque científico do uso da informação médica – Medicina Baseada em Evidência. Série Estudos em Saúde Coletiva. 1998;8:1–27.

Nadanovsky P, Carvalho LM. Prevalence of oral malodour in the family of university students. J Dent Res. 2000;79:380.

Onozawa H, Yasui T, Nakao S-I. A study of the relationship between oral parameters and breath odour. In: Van Steenberghe D, Rosenberg M, editors. Bad breath: a multidisciplinary approach. Leuven: Leuven University Press; 1996. p. 195–8.

Preti G, Clark L, Cowart BJ, Feldman RS, Lowry LD, Weber E, Young IM. Non-oral etiologies of oral malodor and altered chemosensation. J Periodontol. 1992;63:790–6.

Queiroz CS, Tabchoury CM, Fujimaki, et al. Volatile Sulphur compounds (VSC) in the mouth air in two stressful conditions. J Dent Res. 2000;79:221.

Rosenberg M. Clinical assessment of bad breath: current concepts. JADA. 1996;127:475–82.

Rosenberg M, Kozlovsky A, Wind Y, Mindel E. Self-assessment of oral malodor 1 year following initial consultation. Quintessence Int. 1999;30:324–7.

Rosenberg M, Kulkarni GV, Bosy A, McCulloch CA. Reproducibility and sensitivity of oral malodor measurements with a portable sulphide monitor. J Dent Res. 1991a;70:1436–40.

Rosenberg M, Leib E. Experiences of an Israeli malodor clinic. In: Rosenberg M, editor. Bad breath: research perspectives. Tel Aviv: Ramot Publishing, Tel Aviv University; 1995. p. 137–48.

Rosenberg M, Septon I, Eli I, Bar NR, Gelernter I, Brenner S, Gabbay J. Halitosis measurement by an industrial sulphide monitor. J Periodontol. 1991b;62:487–9.

Salvador SL, Figueiredo LC. Halitosis and periodontal disease in Down's syndrome, mentally retarded and healthy patients. J Dent Res. 2000;79:2053.

Schmidt NF, Missan SR, Tarbet WJ. The correlation between organoleptic mouth-odor ratings and levels of volatile sulfur compounds. Oral Surg Oral Med Oral Pathol. 1978;45:560–7.

Schubert TT, Schubert AB, Ma CK. Symptoms, gastritis, and Helicobacter pylori in patients referred for endoscopy. Gastrointest Endosc. 1992;38:357–60.

Shimura M, Watanabe S, Iwakura M, Oshikiri Y, Kusumoto M, Ikawa K, Sakamoto S. Correlation between measurements using a new halitosis monitor and organoleptic assessment. J Periodontol. 1997;68:1182–5.

Smith R. Where is the wisdom? The poverty of medical evidence (Editorial). BMJ. 1991;303(6806):798–9.
Tiomny E, Arber N, Moshkowitz M, Peled Y, Gilat T. Halitosis and helicobacter-pylori – a possible link. J Clin Gastroenterol. 1992;15:236–7.
Tonzetich J. Direct gas chromatographic analysis of sulphur compounds in mouth air in man. Arch Oral Biol. 1971;16:587–97.
Tonzetich J, Ng SK. Reduction of malodor by oral cleansing procedures. Oral Surg Oral Med Oral Pathol. 1976;42:172–81.
Tydd TF, Dyer NH. Pyloric stenosis presenting with halitosis. Br Med J. 1974;3:321.
U.S. Preventive Services Task Force. Appendix A: tax force ratings. In: U.S. Preventive Services Task Force, editor. Guide to clinical preventive services. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 1996. p. 861–85.
Yamaga T, Miyazaki. Usefulness of VSC measurements on screening for predicting the progress of periodontal disease. In: Hoshi K, Kawaguchi Y, Matsuo T, et al., editors. Proceedings of the fifth international conference on breath odor, July 1–2, 2001, Tokyo, Japan. Tokyo: International Society for Breath Odor Research and the National Center of Science; 2001. p. 62.

Further Reading

Nadanovsky P, Britto SH. Hálito: passo a passo para um hálito agradável. Rio de Janeiro: E-papers. 2007. http://www.e-papers.com.br/ or http://www.e-papers.com.br/produtos.asp?codigo_produto=1036&promo=0.
Scully C, Greenman J. Halitology (breath odour: aetiopathogenesis and management). Oral Dis. 2012;18:333–45.
Seemann R, Conceicao MD, Filippi A, Greenman J, Lenton P, Nachnani S, Quirynen M, Roldan S, Schulze H, Sterer N, Tangerman A, Winkel EG, Yaegaki K, Rosenberg M. Halitosis management by the general dental practitioner-results of an international consensus workshop. J Breath Res. 2014;8:017101.

Oral Lesions in Soft Tissues

Sandra Beatriz Chaves Tarquinio, Marco A. Peres, Luísa Jardim Corrêa de Oliveira, and Karine Duarte da Silva

Contents

15.1 Introduction – 252

15.2 Methodologies of Data Collection and Analysis of OML – 252
15.2.1 Clinical Examination – 252
15.2.2 Instruments of Measurement of the Occurrence of OML – 253
15.2.3 Limitations – 254

15.3 Studies on OML Prevalence – 255
15.3.1 Children and Adolescents – 255
15.3.2 Young and Middle-Aged Adults – 256
15.3.3 Old People – 257

15.4 The Use of Technology in Population-Based Epidemiological Studies – 258

15.5 Final Considerations – 260

References – 261

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_15

Learning Objectives

- Highlight the main methodologies used in studies about the prevalence of oral lesions in soft tissues
- Present the main results of studies on the prevalence of oral lesions in soft tissues in the different age groups
- Point out new possibilities of using technologies in the service of epidemiological studies on oral lesions in soft tissues

15.1 Introduction

Epidemiological studies on the prevalence of *oral lesions* aim to depict the burden of disease in a previously specified population group, time, and place. Such information is necessary for health policy and planning, and the diagnosis of a wide variety of lesions occurring in the oral mucosa is an essential part of dental practice.

Preventing early diagnosis and appropriate treatment of *oral lesions in soft tissues*, also called *oral mucosal lesions* (OML), requires a detailed knowledge of the changes affecting the stomatognathic system, including its etiological aspects and major risk factors. Some types of OML may cause pain and can lead to some difficulties in eating, speaking, and laughing, and, recently, it has been reported that the oral health-related quality of life (OHRQoL) of children, adolescents, and adults could be impacted by the presence of the OML [1–4].

Population-based studies on the prevalence of OML are scarce but very useful, as they provide a detailed description of the epidemiology of these nosological conditions, revealing relevant oral health characteristics of specific population groups. Most epidemiological studies on *oral lesions* use convenience samples to study specific population groups, with certain demographic, but few are population-based [5–7].

This chapter was divided into sections: to highlight the main methodologies of OML collection and analysis, to present the main results of the studies on the prevalence of OML in the different age groups, and to point out new possibilities for the use of technologies in the service of epidemiological studies on OML.

> Mouth lesions are conditions that affect the soft tissues of the mouth, recognized as different type of lesions that are expressed by various clinical aspects such as color changes, solid formations, fluid collections, and loss of tissue [8]. These changes may be due to infectious diseases (viruses, fungi, bacteria), local trauma or irritation, and manifestations of systemic diseases (metabolic or immunological). They can also be related to habits and lifestyle [9].

15.2 Methodologies of Data Collection and Analysis of OML

Factors such as the determination of the sample size, the establishment of diagnostic criteria, the training and calibration of the professionals involved in the study, whether examiners or interviewers, as well as aspects related to the standardization of the tests and examination are critical points about the epidemiology of *oral lesions*. Epidemiological studies of OML require rigorous standardization of their methods to be reproducible and comparable one with each other.

15.2.1 Clinical Examination

Data collection of OML includes a detailed and standardized clinical examination. The World Health Organization provides a manual entitled *Oral Health Surveys – Basic Methods*, published in 2013 [10], which is a very important tool to be used as a guide for the good conduction of epidemiological studies.

The instruments and supplies needed for the clinical examination of the oral cavity, such as mouth mirrors, periodontal probe, and gauzes, must be sterilized and in sufficient quantity so that the examinations can be performed uninterrupted. Wooden spatulas can also be used to move the oral soft tissues. Periodontal probes or flexible plastic school rules may be used to measure the lesions of the oral mucosa. The use of disposable gloves, masks, and caps and wearing of protective glasses are strongly recommended.

Clinical examination does not necessarily have to be performed in a dental office, it can be done in research centers, schools, participants´ home, and even outside, as long as the biosafety measures are followed and the patient is minimally comfortable, positioned in a chair, table, or even on the floor lying on a cloth. It is also important that the illumination of the oral cavity is adequate, in order to facilitate the detection of oral disorders. Headlights may be used, which also favors the standardization of the examinations, since different conditions of luminosity may be observed, depending on the place where the examination is done.

It is important to follow a sequence when performing the clinical examination, in order to do not forget any important region, as well as to make the process faster. WHO recommends the following sequence:

1. Labial mucosa and labial sulci (upper and lower)
2. Labial part of the commissures and buccal mucosa (right and left)
3. Tongue (dorsal and ventral surfaces, margins)
4. Floor of the mouth
5. Hard and soft palate
6. Alveolar ridges/gingiva (upper and lower)

It is recommended to refer to the aforementioned WHO guide for further details on the entire process of planning and conducting clinical examinations.

15.2.2 Instruments of Measurement of the Occurrence of OML

Not only the clinical examination is important to collect data about OML. Questionnaires can also be used after appropriate training of interviewers, searching for aspects like symptomatology, time of evolution of the lesions, and oral self-examination, for example. It is important that the questions included in the questionnaires are validated in previous studies. The questionnaires used in the well-known Pelotas cohort studies (Brazil) are recommended as references and can be found on the website ► www.epidemio-ufpel.org.br.

Regarding the criteria to classify the oral conditions detected in epidemiological studies, those established by WHO in 2013 [10] are recommended, as gold standard, according to the following clinical (presumptive) diagnoses and codes:

- 0 = No abnormal condition
- 1 = Malignant tumor (oral cancer)
- 2 = Leukoplakia
- 3 = Lichen planus
- 4 = Ulceration (aphthous, herpetic, traumatic)
- 5 = Acute necrotizing ulcerative gingivitis (ANUG)
- 6 = Candidiasis
- 7 = Abscess
- 8 = Other condition (specify if possible) (e.g., keratosis and Koplik spots)
- 9 = Not recorded

In 1980, an important guide was published by WHO for conducting epidemiology studies of *oral mucosal diseases* and conditions [11]. The clinical diagnoses included in that guide were a quite different from the WHO guide from 2013 [10], but the authors in that time already pointed that adaptations could be made, according to particular interests of research and characteristics of the studied population. The authors of this chapter stimulated to follow the WHO guides, performing the adaptations recommended by WHO/1980 [11], with rigorous criteria and based on the aspects already mentioned.

Additionally to clinical diagnoses, the main locations of the lesions found comprise, according to WHO recommendations [10]:

- 0 = Vermillion border
- 1 = Commissures
- 2 = Lips
- 3 = Sulci
- 4 = Buccal mucosa
- 5 = Floor of the mouth
- 6 = Tongue
- 7 = Hard and/or soft palate
- 8 = Alveolar ridges/gingiva
- 9 = Not recorded

Epidemiological studies involving more than one observer demand the assessment of concordance inter- and intra-examiners. A reliable and standardized diagnosis can be obtained by calibrating the examiners who will participate in epidemiological studies [8, 12, 13]. This process can be done through clinical examinations in a population with a similar profile to the one that will be investigated [12], but it may be difficult to find a sufficient number of *oral lesions* for satisfactory calibration. Thus, strategies such as in lux calibration [8], that comprises an initial theoretical approach and, after that, photographs of the lesions under investigation, are presented to the examiners, who are so evaluated for their recognition, and the concordance between them is checked. A satisfactory reproducibility between the different examiners must be aimed (Kappa superior to 0.6). The training and calibration are important steps to identify diagnostic problems, discuss protocols, and minimize differences between examiners.

Oral health studies performed in the live-birth cohorts of 1982 at 24 years of age and 2004 at the age of 5 in the city of Pelotas [3, 8] assessed several oral conditions such as dental caries, periodontal disease, malocclusion, and OML. The last were categorized according to their main characteristics (type of lesions), in detriment of the clinical diagnosis, due to the limitation of having not obtained a satisfactory agreement between the examiners, in both studies during the calibration phase. Thus, the clinical aspect of the lesion (papule, nodule, ulcer, vesicle, bubble, plaque, or erosion) was recorded in order to minimize disagreements and increase the reliability of the study.

However, in the last two surveys in Pelotas cohorts (1982 cohort at 31 years of age and in pregnant mothers of subjects belonging to the 2015 cohort), in which OML were investigated, after reflecting about the criteria of classification of the lesions and confronting with the literature and background accumulated about the subject, it was decided to investigate the lesions through clinical diagnoses, since after calibration of the examiners, a satisfactory value of repeatability and reproducibility was obtained. These studies are now being drafted for publication.

Points of Emphasis

Diagnostic criteria according to the clinical diagnoses [10]:

- No abnormal condition
- Malignant tumor (oral cancer)
- Leukoplakia

- Lichen planus
- Ulceration (aphthous, herpetic, traumatic)
- Acute necrotizing ulcerative gingivitis (ANUG)
- Candidiasis
- Abscess
- Other condition (specify if possible)
- Not recorded

Points of Emphasis

Diagnostic criteria according to the type of lesions [3, 6, 8, 9]:

- Papule or nodule (superficial or deep solid and circumscribed elevations of the mucosa, differing by the size)
- Ulcer (open sores inside the mouth)
- Vesicle or bubble (circumscribed elevation of the oral mucosa containing liquid material; differing by the size)
- Plaque (elevation of oral mucosa, whose height is lower than its length)
- Erosion (partial epithelial loss is observed)

15.2.3 Limitations

Comparative analyses between the various epidemiological studies of OML are difficult because of some factors as follows: (a) differences in study design and methods of data gathering; (b) variation of age groups in the different studies; (c) classification of the lesions into non-uniform categories; (d) problems involving the lack of training and calibration of examiners; and (e) geographic and cultural differences between populations that may influence the prevalence of the lesions. All these aspects were discussed in a systematic review by authors of this chapter, which is under review for publication.

Regarding the study design and the determination of sample size, few assessments have random samples [14–16], the majority of them coming from pre-selected groups such as those related to health services, hospitals, clinics, day care centers, shelters for the elderly, and others [17–19]. The limitations of these studies as it is not possible to extrapolate the data to the general population should be considered when comparing their data with the prevalence of *oral lesions* estimated using population-based samples.

Variation of the age range in different population groups studied also make it difficult to compare epidemiological indicators of OML among individuals who participated in studies whose target population were heterogeneous regarding age since certain lesions predominate in different phases of life. The manifestations of primary herpes, for instance, are more common in children under 5 years of age, whereas squamous cell carcinoma mainly affects adult males over 45 years of age, and the Burning Mouth Syndrome is more prevalent in middle-aged women in the period of the menopause [9]. Therefore, it is important select the lesions that will be evaluated in the studies taking into account the age of the population under investigation. The participation of a specialist in oral medicine is recommended in this process. The World Health Organization (WHO) recommends the assessment of the following age groups: 5, 12, 15, 35 to 44, and 65 to 74 years old [10].

Two main ways of classifying the OML are observed: according their clinical aspect or type of lesion [3, 6, 8] and through clinical diagnosis [5, 12, 13, 20–22]. The majority of epidemiological studies use the last approach, which is more accurate and better represents the clinical condition found. A wide range of clinical diagnosis can be found in the oral cavity. These diagnoses are often grouped for better visualization of the data [5, 6, 12, 22].

However, the groups observed in the studies are not standardized, making it difficult to interpret and compare results between them. Some studies classify the lesions according to their nature (infectious, pigmented, tumor and tumor-like lesions, salivary gland diseases, denture-related lesions, developmental conditions) [23–25], other by surface color and appearance (white and red lesions, ulcers, raised conditions) [5, 21, 22], generating a considerable heterogeneity between studies. As there is no standardization and recommendation in this sense, the presentation of the results by groups, but also by individual, clinical diagnoses may be a way of promoting comparisons and better visualization of which nosological entities are more frequent in each group.

Another important point to be considered is the inclusion of clinical diagnoses of transient and recurrent lesions such as recurrent herpetic lesions and aphthous stomatitis. Their occurrence may appear overestimated if they are eventually present at the clinical examination [20]. Some studies choose to verify its occurrence also by self-reported lifetime history. However, data related to self-report may be underestimated, being of little value in some cases, as in childhood or individuals with intellectual or cognitive impairments. Although these conditions are not of significant clinical relevance, the WHO recommends their inclusion in the studies, and their results should be observed with caution regarding the prevalence of the lesions investigated.

Similarly, developmental defects or variations in normality, such as Fordyce granules, fissured and geographic tongue, and exostosis, are present in many epidemiological studies [5, 13, 20, 21], even though they are not included in the clinical diagnoses recommended by the WHO manual. These conditions are of relatively common occurrence and when included in the investiga-

tions usually present high prevalence in relation to the others, which should be analyzed with caution. Although with little relevance in terms of oral health, usually not requiring any treatment [8], its inclusion in future studies should be considered for better comparability with previous ones.

A systematic review published in 2006 included 29 studies about the prevalence of some injuries in children and adolescents and revealed that few of them were satisfactorily comparable in terms of methodology, being observed considerable variation related to the diagnostic criteria and method of detection employed, additionally to the lack of information regarding these aspects in many studies [26]. These findings demonstrate that the standardization of methodologies in epidemiological studies about OML needs to be improved.

► Box 15.1 summarizes important methodological aspects of population-based studies on OML.

Box 15.1 Summary of the main methodological aspects of population-based studies on OML

Important reference to be adopted	Clinical diagnoses included (WHO 2013)	Sequence of oral clinical examination (WHO 2013)	Main locations (WHO 2013)	Taking care when comparing studies
Oral Health Surveys – Basic Methods (2013), by World Health Organization (WHO)	0 = No abnormal condition 1 = Malignant tumor (oral cancer) 2 = Leukoplakia 3 = Lichen planus 4 = Ulceration (aphthous, herpetic, traumatic) 5 = Acute necrotizing ulcerative gingivitis (ANUG) 6 = Candidiasis 7 = Abscess 8 = Other condition (specify if possible) (e.g., keratosis and Koplik spots) 9 = Not recorded	1 = Labial mucosa and labial sulci (upper and lower) 2 = Labial part of the commissures and buccal mucosa (right and left) 3 = Tongue (dorsal and ventral surfaces, margins) 4 = Floor of the mouth 5 = Hard and soft palate 6 = Alveolar ridges/gingiva (upper and lower)	0 = Vermillion border 1 = Commissures 2 = Lips 3 = Sulci 4 = Buccal mucosa 5 = Floor of the mouth 6 = Tongue 7 = Hard and/or soft palate 8 = Alveolar ridges/gingiva 9 = Not recorded	1 = Age range 2 = Diagnostic criteria 3 = Geographic and cultural differences between populations

15.3 Studies on OML Prevalence

15.3.1 Children and Adolescents

Studies assessing the prevalence of *oral lesions* in children are heterogeneous with respect to the age range. The lack of uniform methodological criteria explains most of the variation in the prevalence of *oral lesions* among studies worldwide. Moreover, some approaches have retrospectively analyzed data from archives of clinical and histopathological diagnostic services [27]. Other studies used an epidemiological approach for estimating the prevalence of *oral lesions* in the general population [3, 13]. It is important to identify the distribution of oral diseases by age, from birth to early adulthood, bearing in mind the likelihood of pathological changes to increase with age [28].

The most frequent conditions affecting the oral mucosa of children are recurrent aphthous stomatitis, herpes labialis, fissured tongue, geographic tongue, tongue blisters, oral candidiasis, and traumatic lesions [20, 22, 26, 28]. Lingual conditions, as flaccid, geographic, and fissured or scrotal tongue, are not pathological processes per se. Therefore, some studies do not consider them as *oral lesions*, in order not to overestimate the prevalence of *oral lesions* in this age group [7]. Contrariwise, the majority of authors include these conditions in their assessments, justifying that their high frequency in children and adolescents is noteworthy, even if they do not imply treatment needs [4, 20, 28].

Epidemiological studies in children usually refer to school age. Surveys of newborn infants [29] or preschool children [3] are scarce. However, many studies assessed a broader age range with data previously gathered by

health-care units that provide diagnosis or treatment for *oral lesions*.

Similarities between the prevalence of *oral lesions* in the child population are observed, for example, between Spain, South Africa, Argentina, and Mexico. Studies in the USA, however, showed a divergent prevalence, which is probably due to different clinical diagnostic criteria and the types of samples used. One example that illustrates this heterogeneity is the frequent occurrence of focal epithelial hyperplasia in Brazilian Indians living in a community in the Amazon, a relatively rare condition in other countries [30]. Likewise, commissural pits are common in South Africa [31], Argentina [32], and Mexico [33], but they are not in other countries.

The literature shows timidly the association of OML with lifestyle, specific racial/ethnic characteristics, and environmental factors in children and teenagers [13]. This relationship should be better explained for the real understanding of the social determinants of health in the occurrence of lesions of the oral mucosa, allowing the formulation of strategies for facing the condition.

15.3.2 Young and Middle-Aged Adults

Occurrence of *oral lesions* increases with aging [28], a fact that can be explained by the chronic exposure to sunlight, tobacco, and alcohol, during the lifetime, as well as by the use of prosthesis and the oral manifestations of systemic diseases, such as diabetes [5, 8, 23].

This long-term exposure to carcinogens may lead to a malignant transformation of the oral mucosa, mostly represented by squamous cell carcinoma (SCC), a pathological condition that can be preceded by a potentially malignant disorder, which clinically may be seen as a whitish plaque (leukoplakia), associated or not with a red area (erythroplakia) [34].

The overall prevalence of oral potentially malignant disorders worldwide was 4.47%, with an expressive prevalence rate in populations of Asia, South America, and the Caribbean [35]. Variation occurs in different countries, in different regions of the same country, and also in the same population. This fact can be attributed to methodological differences between studies, such as different diagnostic criteria and target populations, and also to the habits related to its main etiology: tobacco smoking and chewing [35, 36].

In South Asian countries such as India, Pakistan, Sri Lanka, Papua New Guinea, Myanmar, Thailand, and Mainland China, the chronic use of betel quid, whose main substance with psychoactive principle is areca nut, has been considered a potent risk factor for developing SCC. The quid typically consists of associating the betel leaf by wrapping a mixture of areca nut, moistened with lime, usually added with tobacco and sometimes adding sweet condiments. When chewed, this mixture releases areca nut alkaloids, which induce a feeling of euphoria and well-being in the user. Chewing betel quid frequently results in the onset of potentially malignant lesions known as submucosal fibrosis, whose malignant transformation rate in India was estimated to be 7.6%. Among Malaysians, the habit of chewing betel is more prevalent among adult women, over 40 years of age, being a habit of the older generations. A multicenter study in Southern Africa of factors influencing the cessation of this habit revealed that women, often housewives, experiencing financial or family problems and residing in the countryside, where the habit of chewing this mixture is culturally very ingrained, are the population group least likely to abandon it. Also, smoking individuals were more likely to start this habit. Individuals that include areca nut and tobacco in the chewing mixture have revealed to be less inclined to abandon the habit, due to the areca properties of stimulating the parasympathetic nervous system and inducing well-being and the chemical dependence of tobacco nicotine. Health promotion programs aimed at encouraging the abandonment of this habit, which is carcinogenic, rely on the knowledge of the previously described aspects.

A cross-sectional population-based study developed in the metropolitan region of a city in Southern Brazil evaluated the prevalence of *oral lesions* in a predominantly adult population and found a large proportion of conditions demanding some treatment, such as candidiasis, proliferative non-neoplastic lesion, and fistulas. Smoking and alcoholism were associated with the prevalence of potentially malignant lesions [12]. A similar study conducted in Turkey revealed that pigmentation, fissured tongue, and denture stomatitis were observed to be the most common lesions in that population [23]. Almost 42% of the participants had at least one *oral pathology*, a finding that should be considered with caution, in view of the fact that developmental conditions were included, and they were responsible for a large part of this high prevalence.

Tarquinio et al. [8] found a prevalence of 23.3% OML, assessed by type and not by clinical diagnosis, and they did not include developmental changes in that time. Another study shows a general prevalence of 10.8%, even with the inclusion of developmental alterations, such as fissured tongue, the most prevalent lesion. The authors also reviewed the literature about OML and verified a wide variation in prevalence ranging from 5% to 65% [5]. Therefore, it is remarkable that the comparison between studies is quite difficult, taking into account this wide range of values. Aspects referring to study design, especially in relation to the diagnoses included, also geographic and cultural characteristics of

the populations under investigation are important points to be considered.

Diabetes mellitus (DM), a disease which is more prevalent among adults, is strongly associated with the prevalence of some oral conditions, such as stomatitis related to the use of prostheses, angular cheilitis, periodontal disease, caries, decreased salivary flow, and lichen planus. Metabolic alterations related to DM may explain the higher likelihood of these oral conditions. The decreased salivary flow and low pH may lead to inflammatory complications of the oral mucosa, such as stomatitis, angular cheilitis, and glossitis. The cause of the increased prevalence of geographic tongue in diabetic patients is still unknown. Microangiopathy and the delay in tissue repair in DM may be contributing factors for the appearance of glossitis. Lichen planus, a condition whose classification as a premalignant condition is debatable, is the only suspected precancerous conditions associate with DM, although the etiopathogenetic mechanism explaining its higher frequency in diabetic adults is uncertain [37].

Another global public health problem affecting the adult population in developed and developing countries is HIV infection. *Oral lesions* associated with this disease are important because they affect the quality of life and they are markers of immunosuppression. Oral manifestations of HIV infection may vary depending on the population studied, diagnostic criteria, socioeconomic conditions, gender, race, immunological status, and type of antiretroviral drug used, among other aspects [38, 39]. The use of highly active antiretroviral therapy (HAART) has decreased the occurrence and the spectrum of oral manifestations in HIV-positive patients, possibly due to the reconstitution of the immune system promoted by the therapy [38]. However, infections by mycobacteria, varicella zoster virus, herpesvirus, and cytomegalovirus may occur as a consequence of exuberant host immunological response to antigenic stimuli, known as immune reconstitution inflammatory syndrome [40, 41].

Salivary gland tumors consist of a complex and heterogeneous group of lesions with varied histopathological features and distinct biological behaviors, representing 3 to 10% of all tumors involving the head and neck region. The literature reports a higher incidence among females and small variations in age. Adults, during their fourth and fifth decades, are at higher risk for benign lesions, being pleomorphic adenoma of the parotid gland the more common neoplasm. Among the malignant neoplasms, adenoid cystic carcinoma and mucoepidermoid carcinoma are the most frequent tumors affecting the salivary glands. The seventh decade of life represents the age group at higher risk, and the most frequent sites are the parotid gland and the submandibular gland, according to different investigations [42].

In summary, OML affecting young and middle-aged adults are usually related to lifestyle and, to a lesser extent, to the systemic health of these individuals. Developmental conditions are also responsible for a large part of the prevalence of oral conditions in this age group. We strength the importance of comparing studies about the prevalence of OML in the light of their varied methodologies and cultural and geographical differences between populations.

15.3.3 Old People

Probably, one of the most important changes in the distribution of the global population has been the growth of the elderly people, mainly in the developed countries. Brazil is expected that individuals over the age of 65 years represent the population group with the fastest increase and also is expected to become the sixth largest elderly population in the world [43]. This increase in the elderly population has been accentuated since the 1950s, principally because of improved living conditions, the decrease of the infantile mortality, and the mortality from infectious diseases [43]. Therefore, with the extension of the life expectancy, the prevalence of lesions affecting the mouth of the elderly population arises a growing interest.

Such assessments involve population-based studies, cohorts, and cross-sectional studies of institutionalized old people. Information provided by histopathology services around the world has also been used to assess the prevalence of lesions that affect the bucomaxillofacial system of the older population.

A spectrum of situations and events lead to changes in oral mucosa in elderly, being the denture-associated lesions one of the most common type of oral mucosal alterations [44], among other diseases, such as infections, physical causes, changes to the immune system, systemic diseases, and neoplasia [45].

The main lesions that affect individuals using partial or total prostheses are inflammatory fibrous hyperplasia, ulcers, and frictional keratoses, all due to the trauma of ill-fitting prosthetic devices or with suction chamber and defects in the manufacture of oral prostheses and their interaction with the bone and mucosa tissues of the maxillary processes. Other denture-associated lesions are fungal stomatitis such as chronic atrophic candidiasis and angular cheilitis (caused by loss of vertical dimension). Some authors believe that the incidence of traumatic lesions among females may be due to the fact that they wear their dentures more often for aesthetic reasons [44]. The atrophy of the oral mucosa during or after

menopause may offer little protection against the chronic irritation of an ill-fitting denture [46]. In addition to old age, other factors influence the development of lesions in the oral cavity in this age group: systemic diseases, higher use of drugs and medicines, and poor oral hygiene.

Smoking also shows cumulative effects, resulting in nicotinic stomatitis [47, 48] and other oral diseases. Actinic cheilitis, a lesion associated mainly with ultraviolet radiation, also is common in elderly, since the aged individuals are exposed for a long period of time in life to the risk factor [47, 48].

Fibromas and salivary gland neoplasms are benign lesions that deserve prominence due to their relatively high frequency. Malignant neoplasm is also relevant in this population group, mainly tumors originating from the epithelium that covers the oral mucosa (squamous cell carcinoma) and the glandular epithelium. The group of potentially malignant lesions (predominantly leukoplakia and erythroplasia), whose histopathological diagnosis refers to epithelial dysplasias, must also be highlighted. These conditions may be more incident in old age due to the physiological reduction of the protective function of the oral mucosa in old age.

Therefore, the majority of OML observed in elderly are typically considered chronic; their causes may be largely avoidable and can be controlled through educational strategies with adequate psychological and physical health orientation for the patients. Moreover, given that oral changes in old people may interfere with their quality of life, reporting their prevalence may instruct health authorities to implement social and health programs specifically aimed at this preventing and treating these conditions in this population, both those living in the community and those living in nursing homes or hospitals. Therefore, regular oral examination by dentists and oral medicine specialists must be part of geriatric medicine services.

15.4 The Use of Technology in Population-Based Epidemiological Studies

The field of health sciences in modern times counts with the improvement of new technologies, which are distributed in different areas ok the knowledge.

One important contribution is the increasing advancement of molecular biology, a tool that has been used as a source of information in epidemiological studies. Some genetic factors and their interactions with the environment have been investigated for their possible association with morbidities. DNA specimens have begun collecting in large epidemiologic studies and surveys, in order to study genetic risk factors for common diseases. Depending on the study necessity, the type of the appropriated specimens for epidemiologic studies is chosen, in accordance with factors such as the quality and quantity of DNA, convenience of collection and storage, cost, and ability to accommodate future needs for genotyping [49]. The banks of DNA can be stored as followed: (1) dried blood spots; (2) whole blood from which genomic DNA is isolated, (3) immortalized lymphocytes obtained from whole blood or separated lymphocytes, prepared immediately, or cryopreserved; and (4) buccal epithelial cells collected by cytobrush or other ways.

Regarding oral cancer and lesions with malignant potential, the investigation of molecular markers and genetic polymorphisms plays a significant role, since the cumulative exposure to chemical carcinogens acts by modifying the cellular gene structure, with a direct implication in carcinogenesis. Thus, the progression of most tumor types involves the acquisition of genetic and epigenetic alterations in tumor suppressor genes and oncogenes.

Genetic alterations have been studied, such as the homozygous deletion of the gene encoding the GSTM1 enzyme; mutations in the p53 gene, important tumor suppressor; mutations in members of the Ras family; and homozygous deletions and methylations in the p16 tumor suppressor gene. HPV family viruses (HPV16, HPV18, HPV31, HPV33, and HPV45) have been consistently incriminated in the induction of carcinogenesis since the E6 protein of this virus forms a complex leading to the degradation of p53, inhibiting apoptosis. Also, the viral E7 protein destroys the active retinoblastoma (Rb) tumor suppressor gene, leading to increased DNA synthesis and cell proliferation. Cells in the basal layer of the cervical epithelium are known to be targets of these viral interactions. Some studies in this field are summarized in the ► Box 15.2.

Another important and revolutionary tool used in health sciences and more recently in dentistry is related to information technology and telecommunication technology in health-care fields. The so-called “Teledentistry”, a new term that is gaining visibility and attention in the last decades, has a broader meaning today than at its first use in 1997, by Cook [50], when was defined as “the practice of using video-conferencing technologies to diagnose and provide advice about treatment over a distance” and having broader signification than its one of the first uses in 1997, by Cook [50], when was defined as ”the practice of using video-conferencing technologies to diagnose and provide advice about treatment over a distance”. Even the author stated, in that time that video-conferencing was not an essential part of the system, but it had played a significant role in training and maintaining the motivation of the general dentists participating in that pilot study, allowing them to refer a patient and learn how to treat more complicated orthodontic cases. Therefore, in a broader manner, teledentistry is defined as the use of information technology

Box 15.2 Some examples of studies in molecular biology of oral diseases around the world

Genetic/epigenetic alteration	Effect	Oral disease	Authors/country	Type of study
Homozygous deletion of GSTM1 gene	Inactivity of the enzyme that protects the DNA from damage caused by tobacco products	OSCC and leukoplakia	Zhuo [58]/China	Systematic review with meta-analyses
Mutation and polymorphisms in P53	Lack of control of cell proliferation, facilitating tumor development	Head and Neck SCC Cancer in general Potentially malignant lesions in upper aerodigestive tract	Shen [59]/USA Wibley [60]/UK Szymanska [61]/ multicenter study	Service-based Review of the literature Population-based
Mutations in Ras oncogene family (HRas, KRas, and NRas)	Affects cell growth, differentiation, and apoptosis	OSCC	Murugan [62]/Vietnam	Service-based
DNA methylation	Epigenetic modifications contribute in early and later phases of OSCC malignant transformation	OSCC and potentially malignant oral lesions	Mascolo [63]/Italy	Review of the literature
Homozygous deletions and methylations of p16 P16 methylation (P16M)	The association of p16CDKN2A gene methylation with smoking, family history of cancer and survival is dependent on age Total-P16M, including true-P16M and P16H (hydroxymethylation), is consistently and significantly linked to malignant transformation of epithelial dysplasia (ED)	Head and neck tumors Mild or moderate OED (oral leukoplakia, lichen planus, or discoid lupus erythematosus	Farias [64]/Brazil Liu [65]/China	Service-based Service-based
EGFR gene amplification	Two-thirds of the EGFR gene copy number alterations in lymph node metastasis or recurrent tumors can be predicted from the analysis of primary tumors	Primary OSSC, metastatic lymph nodes, and recurrent and multiple primary tumors	Huang [66]/Taiwan	Service-based
HPV 16 and 18	High-risk HPV infection may not be a significant factor in the initiation of the premalignant oral lesions but, instead, may be a later event in the oncogenesis of OSCC	Nonmalignant oral lesions (chronic inflammation, submucous fibrosis, leukoplakia, and squamous papilloma)	Chen [67]/Taiwan	Service-based
Senescence genes (cyclin D1, Rb, maspin, p53, and mouse double minute 2 (MDM2)	A higher frequency of expression of markers of the p16-pRb pathway (cyclin D1, Rb and maspin) in OLD lesions compared to OSCC lesions appears to corroborate the tumor suppressor role of cell senescence. Only Maspin demonstrated statistically significant differences, supporting its value as a prognostic marker in oral precancer. The expression of p53 and MDM2 was significantly higher in lOLD than in healthy oral mucosa, suggesting a correlation of these early markers with early events in oral carcinogenesis	Leukoplakia with dysplasia (OLD+) and OSCC	Martinez [68]/Spain	Service-based

and telecommunications for oral care, consultation, education, and public awareness, similarly to telehealth [51].

Teledentistry can be also used in formal online education, being divided into two main categories: web-based self-instruction and interactive video-conferencing. The first educational system contains information that has been developed and stored before the users accesses the program, which provides them the control of learning and allows to review the material as many times as they wish or need [52]. However, the lack of face-to-face communication among the instructors and peers generates dissatisfaction and reduces the accuracy of the diagnosis of OML [53]. Having in mind this point of view, the interactive video-conferencing system is more effective than web-based system because of its ability to provide feedback for the users [53].

In general, the main benefits of the use of communication technology in dentistry are according to Daniel and Kumar [51]: (1) faster access to oral health care; (2) improvement of quality care; (3) improvement of professional education; (4) convenient and time-saving for patients; (5) decreasing of the inequities of access to care and specialists, especially in rural areas from countries in developing world; (6) reduction of health-care access; (7) increasing access among primary, secondary, and tertiary care; and (8) providing quality control of screening programs.

However, as this technology is relatively new, the same authors [51] pointed some obstacles to implement teledentistry, such as (1) the impossibility of performing the whole consultation; (2) the changes in acquiring knowledge and skills by the health professionals; (4) modifications in ergonomic issues; (5) feeling of lack of confidence by the patients and professionals, due to the new approaches; and (6) organizational and bureaucratic barriers that need to be overcome, like infrastructure planning and development, absence of consistent policies that regulate the telecommunications activities, licensure and credentialing of professionals, medical malpractice liability due to uncertain legal regulations in this field, and lose of confidentiality, due to unauthorized access to patients data.

The interaction between the user and an expertise in teledentistry can be exchanged in different ways, being or prerecorded and storage (in an offsite or clouds computing) or obtained in real time [51]. The users can communicate through computers, smart phones, and tablets, with the medium of communication based on (a) satellite, (b) terrestrial telephone lines, (c) integrated service digital network (ISDN) – wireless-based, and (d) combined technologies.

Since this approach is new, there are very little evidence accumulated about its effectiveness [51]. However, some promising initiatives applying this technology have been experienced in Brazil, like the use of telediagnosis of oral mucosal lesions [54, 55], which have potential to improve the oral lesion diagnosis and management in the public health services. Perhaps, teledentistry may be a useful tool in epidemiologic studies, facilitating the calibration systematic between the examiners and the expertise and allowing the first to communicate with the gold standard professionals and solve doubts about the diagnosis of mucosal *oral lesions*, during the field work.

The literature has pointed other specific technologies at assisting clinicians in identifying oral cancer and potential malignant *oral lesions*, such as autofluorescence, in order to improve detection of these lesions in different population groups [56], or to analyze collected buccal cells from epidemiologic surveys [57].

Therefore, the new technologies are valuable tools that can improve and qualify the epidemiologic studies, providing a variety of new data analysis and contributing with the correct diagnosis of the OML.

15.5 Final Considerations

Assessing the prevalence of *oral lesions* in a given population over a given period provides important subsidies to the planning of strategies and programs aimed at the prevention and treatment of these diseases, some of which are considered public health problems. The distribution and prevalence of OML around the world are quite heterogeneous.

The epidemiological study of these diseases faces several difficulties, because there are no standardized methods for data collection and the categories used in the classification of these lesions are not systematized, which hinders the calibration of examiners and makes difficult the statistical comparison.

Due to the observed differences in the frequency of lesions according to the population group, the sections of this chapter focused on the epidemiological study of these lesions, according to age: children and adolescents, young and middle-aged adults, and old individuals.

Epidemiological investigations conducted in the general population of children cover school age, with few studies assessing newborn or preschool children. The most prevalent conditions in children are changes related to inflammation, infection, and trauma, in addition to anatomical modifications of the tongue.

The number of *oral lesions* increases with age, making the adult population the target of several epidemiological investigations, which must focus on premalignant and malignant conditions, chronic degenerative diseases such as diabetes mellitus, and oral manifestations of infection, among others. Summing up, OML affecting young and middle-aged adults are usually related to lifestyle and to the systemic health of these individuals, being the developmental conditions also responsible for

an important increase in the prevalence of oral conditions in this age group.

In old age, the majority of OML observed are typically considered chronic. Some of the problems of adult life aggravate, and other pathological changes appear in the oral mucosa, such as those directly associating with the use of a dental prosthesis. Other factors, such as infections, physical causes, changes to the immune system, systemic diseases, and neoplasia, need to be considered in respect of the prevalence of OML in elderly.

With the advancement of new technologies, epidemiological studies can also use tools such as molecular biology and teledentistry, among others, in order to improve the understanding of oral problems. These perspectives may result in the search for genetic markers for some diseases, like oral cancer, and also may improve the communication, the education, the velocity, and quality of access of the population to the oral health system.

► Box 15.1 Summary of the main methodological aspects of population-based studies on OML

References

1. Krisdapong S, Sheiham A, Tsakos G. Impacts of recurrent aphthous stomatitis on quality of life of 12- and 15-year-old Thai children. Qual Life Res. 2012;21(1):71–6.
2. Suliman NM, Johannessen AC, Ali RW, Salman H, Åstrøm AN. Influence of oral mucosal lesions and oral symptoms on oral health related quality of life in dermatological patients: a cross sectional study in Sudan. BMC Oral Health. 2012;12(1):1–11.
3. De Oliveira LJC, Torriani DD, Correa MB, Peres MA, Peres KG, Matijasevich A, et al. Oral mucosal lesions' impact on oral health-related quality of life in preschool children. Community Dent Oral Epidemiol. 2015;43(6):578–85.
4. Vieira-Andrade RG, Martins-Júnior PA, Corrêa-Faria P, Marques LS, Paiva SM, Ramos-Jorge ML. Impact of oral mucosal conditions on oral health-related quality of life in preschool children: a hierarchical approach. Int J Paediatr Dent. 2015;25(2):117–26.
5. Feng J, Zhou Z, Shen X, Wang Y, Shi L, Wang Y, et al. Prevalence and distribution of oral mucosal lesions: a cross-sectional study in Shanghai. China J Oral Pathol Med. 2015;44(7):490–4.
6. Do LG, Spencer AJ, Dost F, Farah CS. Oral mucosal lesions: findings from the Australian National Survey of Adult Oral Health. Aust Dent J. 2014;59(1):114–20.
7. Silva LVO, Arruda JAA, Martelli SJ, Kato CNO, Nunes LFM, Vasconcelos ACU, et al. A multicenter study of biopsied oral and maxillofacial lesions in a Brazilian pediatric population. Braz Oral Res. 2018;32(0):1–9.
8. Tarquinio SBC, Oliveira LJC, Correa MB, Peres MA, Peres KG, Gigante DP, Horta BL, Demarco FF. Factors associated with prevalence of oral lesions and oral self-examination in young adults from a birth cohort in Southern Brazil. Cad Saude Publica. 2013;29(1):155–64.
9. Neville B, et al. Oral and maxillofacial pathology. 4th ed. Elsevier: Saunders; 2016.
10. World Health Organization. Oral health surveys: basic methods. 5th ed. Geneva, World Health Organization; 2013.
11. Kramer IR, Pindborg JJ, Bezroukov V, Infirri JS. Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. World Health Organization. Community Dent Oral Epidemiol. 1980 Feb;8(1):1–26.
12. Carrard VC, Haas AN, Rados PV, Filho MS, Oppermann RV, Albandar JM, et al. Prevalence and risk indicators of oral mucosal lesions in an urban population from South Brazil. Oral Dis. 2011;17(2):171–9.
13. Vieira-Andrade RG, Martins-Júnior PA, Corrêa-Faria P, Stella PEM, Marinho SA, Marques LS, et al. Oral mucosal conditions in preschool children of low socioeconomic status: prevalence and determinant factors. Eur J Pediatr. 2013;172(5):675–81.
14. Ikeda N, Handa Y, Khim SP, Durward C, Axéll T, Mizuno T, et al. Prevalence study of oral mucosal lesions in a selected Cambodian population. Community Dent Oral Epidemiol. 1995;23(1):49–54.
15. Splieth CH, Sümnig W, Bessel F, John U, Kocher T. Prevalence of oral mucosal lesions in a representative population. Quintessence Int. 2007;38(1):23–9.
16. Zain RB, Ikeda N, Razak IA, Axéll T, Majid ZA, Gupta PC, Yaacob M. A national epidemiological survey of oral mucosal lesion in Malaysia. Community Dent Oral Epidemiol. 1997;25(5):377–83.
17. Majorana A, Bardellini E, Flocchini P, Amadori F, Conti G, Campus G. Oral mucosal lesions in children from 0 to 12 years old: ten years' experience. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 2010;110(1):e13–8.
18. Mehrotra R, Thomas S, Nair P, Pandya S, Singh M, Nigam NS, Shukla P. Prevalence of oral soft tissue lesions in Vidisha. BMC Res Notes. 2010;3:23.
19. Pentenero M, Broccoletti R, Carbone M, Conrotto D, Gandolfo S. The prevalence of oral mucosal lesions in adults from the Turin area. Oral Dis. 2008;14(4):356–66.
20. Jahanbani J, Douglas E, Morse HA. Prevalence of oral lesions and normal variants of the oral mucosa in 12 to 15-year-old students in Tehran. Iran. 2012;15(3):142–5.
21. Mansour Ghanaei F, Joukar F, Rabiei M, Dadashzadeh A, Valeshabad AK. Prevalence of oral mucosal lesions in an adult Iranian population. Iran Red Crescent Med J. 2013;15(7):600–4.
22. Shulman JD. Prevalence of oral mucosal lesions in children and youths in the USA. Int J Paediatr Dent. 2005;15:89–97.
23. Mumcu G, Cimilli H, Sur H, Hayran O, Atalay T. Prevalence and distribution of oral lesions: a cross-sectional study in Turkey. Oral Dis. 2005;11(2):81–7.
24. Lin HC, Corbet EF, Lo ECM. Oral mucosal lesions in adult Chinese. J Dent Res. 2001;80(5):1486–90.
25. Salonen L, Axéll T, Helldén L. Occurrence of oral mucosal lesions, the influence of tobacco habits and an estimate of treatment time in an adult Swedish population. J Oral Pathol Med. 1990;19(4):170–6.
26. Furlanetto DLC, Crighton A, Topping GVA. Differences in methodologies of measuring the prevalence of oral mucosal lesions in children and adolescents. Int J Paediatr Dent. 2006;16(1):31–9.
27. da Silveira Lima G, Fontes ST, de Araújo LMA, Etges A, Tarquinio SBC, Gomes APN. A survey of oral and maxillofacial biopsies in children: a single-center retrospective study of 20 years in Pelotas-Brazil. J Appl Oral Sci. 2008;16(6):397–402.
28. Amadori F, Bardellini E, Conti G, Majorana A. Oral mucosal lesions in teenagers: a cross-sectional study. Ital J Pediatr. 2017;43(1):1–6.
29. Yilmaz AE, Gorpelioglu C, Sarifakioglu E, Dogan DG, Bilici M, Celik N. Prevalence of oral mucosal lesions from birth to two years. Niger J Clin Pract. 2011;14(3):349–53.
30. dos Santos PJB, Bessa CFN, de Aguiar MCF, do Carmo MAV. Cross-sectional study of oral mucosal conditions among a

central Amazonian Indian community, Brazil. J Oral Pathol Med. 2004;33(1):7–12.
31. Lawoyin JO. Paediatric oral surgical pathology service in an African population group: a 10 year review. Odontostomatol Trop. 2000;23(89):27–30.
32. Keszler A, Guglielmotti MB, Dominguez FV. Oral pathology in children. Frequency, distribution and clinical significance. Acta Odontol Latinoam. 1990;5(1):39–48.
33. Castellanos JL, Díaz-Guzmán L. Lesions of the oral mucosa: an epidemiological study of 23785 Mexican patients. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontol. 2008;105(1):79–85.
34. Warnakulasuriya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125(6):582–90.
35. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, et al. Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. J Oral Pathol Med. 2018;47(7):633–40.
36. Chung CH, Yang YH, Wang TY, Shieh TY, Warnakulasuriya S. Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan. J Oral Pathol Med. 2005;34(8):460–6.
37. Saini R, Al-Maweri SA, Saini D, Ismail NM, Ismail AR. Oral mucosal lesions in non oral habit diabetic patients and association of diabetes mellitus with oral precancerous lesions. Diabetes Res Clin Pract. 2010;89(3):320–6.
38. de Almeida VL, Lima IFP, Ziegelmann PK, Paranhos LR, de Matos FR. Impact of highly active antiretroviral therapy on the prevalence of oral lesions in HIV-positive patients: a systematic review and meta-analysis. Int J Oral Maxillofac Surg. 2017;46(11):1497–504.
39. Peppes CP, Lemos ASP, Araujo RLF, Portugal MEG, Da Cruz M, Buffon M, Raboni SM. Oral lesions frequency in HIV-positive patients at a tertiary hospital, Southern Brazil. Brazilian J Oral Sci. 2013;12(3):216–22.
40. Murdoch DM, Venter WDF, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. AIDS Res Ther. 2007;4:1–10.
41. Tsang CSP, Samaranayake LP. Immune reconstitution inflammatory syndrome after highly active antiretroviral therapy: a review. Oral Dis. 2010;16(3):248–56.
42. de Oliveira FA, Duarte ECB, Taveira CT, Máximo AA, de Aquino ÉC, de Cássia AR, et al. Salivary gland tumor: a review of 599 cases in a Brazilian population. Head Neck Pathol. 2009;3(4):271–5.
43. de Carvalho JAM, Rodríguez-Wong LL. A transição da estrutura etária da população brasileira na primeira metade do século XXI. Cad Saude Publica. 2008;24(3):597–605.
44. Mandali G, Sener ID, Turker SB, Ülgen H. Factors affecting the distribution and prevalence of oral mucosal lesions in complete denture wearers. Gerodontology. 2011;28(2):97–103.
45. Mendes DC, De Oliveira Poswar F, De Oliveira MVME, Haikal DSA, Da Silveira MF, De Barros Lima Martins AME, et al. Analysis of socio-demographic and systemic health factors and the normative conditions of oral health care in a population of the Brazilian elderly. Gerodontology. 2012;29(2):1–9.
46. Buchner A, Calderon S, Ramon Y. Localized hyperplastic lesions of the gingiva: a clinicopathological study of 302 lesions. J Periodontol. 1977;48(2):101–4.
47. Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. Community Dent Oral Epidemiol. 2000;28:390–8.
48. Dundar N, Ilhan KB. Oral mucosal conditions and risk factors among elderly in a Turkish school of dentistry. Gerontology. 2007;53(3):165–72.
49. Steinberg K, Beck J, Nickerson D, Garcia-Closas M, Gallagher M, Caggana M, et al. DNA banking for epidemiologic studies: a review of current practices. Epidemiology. 2002;13(3):246–54.
50. Cook J. ISDN video conferencing in postgraduate dental education and orthodontic diagnosis. Learning Technology in Medical Education Conference 1997 (CTI Medicine). 1997:111–6.
51. Daniel SJ, Kumar S. Teledentistry: a key component in access to care. J Evid Based Dent Pract. 2014;14 Suppl:201–8.
52. Chen JW, Hob-Dell MH, Dunn K, Johnson KA, Zhang J. Teledentistry and its use in dental education. J Am Dent Assoc. 2003;134(3):342–6.
53. Spallek H, Pilcher E, Lee J-YY, Schleyer T. Evaluation of web-based dental CE courses. J Dent Educ. 2002;66(3):393–404.
54. Petruzzi M, De Benedittis M. WhatsApp: a telemedicine platform for facilitating remote oral medicine consultation and improving clinical examinations. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(3):248–54.
55. Carrard VC, Roxo Gonçalves M, Rodriguez Strey J, Pilz C, Martins MAT, Martins MD, et al. Telediagnosis of oral lesions in primary care: the EstomatoNet program. Oral Dis. 2018;24(6):1012–9.
56. Lalla Y, Matias MAT, Farah CS. Oral mucosal disease in an Australian urban indigenous community using autofluorescence imaging and reflectance spectroscopy. Aust Dent J. 2015;60(2):216–24.
57. Paszkiewicz GM, Timm EA, Mahoney MC, Wallace PK, Sullivan Nasca MA, Tammela TL, et al. Increased human buccal cell autofluorescence is a candidate biomarker of tobacco smoking. Cancer Epidemiol Biomark Prev. 2008;17(1):239–44.
58. Zhuo W, Wang Y, Zhuo X, Zhu Y, Wang W, Zhu B, et al. CYP1A1 and GSTM1 polymorphisms and oral cancer risk: association studies via evidence-based meta-analyses. Cancer Investig. 2009;27(1):86–95.
59. Shen H, Zheng Y, Sturgis EM, Spitz MR, Wei Q. P53 codon 72 polymorphism and risk of squamous cell carcinoma of the head and neck: a case-control study. Cancer Lett. 2002;183(2):123–30.
60. Whibley C, Pharoah PDP, Hollstein M. p53 polymorphisms: cancer implications. Nat Rev Cancer. 2009;9(2):95–107.
61. Szymańska K, Levi JE, Menezes A, Wünsch-Filho V, Eluf-Neto J, Koifman S, et al. TP53 and EGFR mutations in combination with lifestyle risk factors in tumours of the upper aerodigestive tract from South America. Carcinogenesis. 2010;31(6):1054–9.
62. Murugan AK, Hong NT, Cuc TTK, Hung NC, Munirajan AK, Ikeda MA, et al. Detection of two novel mutations and relatively high incidence of H-RAS mutations in Vietnamese oral cancer. Oral Oncol. 2009;45(10):e161–6.
63. Mascolo M, Siano M, Ilardi G, Russo D, Merolla F, de Rosa G, et al. Epigenetic disregulation in oral cancer. Int J Mol Sci. 2012;13(2):2331–53.
64. Farias LC, Fraga CAC, Oliveira MVM, Fonseca-Silva T, Marques-Silva L, Moreira PR, et al. Effect of age on the association between p16CDKN2A methylation and DNMT3B polymorphism in head and neck carcinoma and patient survival. Int J Oncol. 2010;37:167–76.

65. Liu H, Liu Z, Liu XW, Xu S, Wang L, Liu Y, et al. A similar effect of P16 hydroxymethylation and true-methylation on the prediction of malignant transformation of oral epithelial dysplasia: observation from a prospective study. BMC Cancer. 2018;18(1):1–9.
66. Huang SF, Chien HT, De Cheng S, Chuang WY, Liao CT, Wang HM. EGFR copy number alterations in primary tumors, metastatic lymph nodes, and recurrent and multiple primary tumors in oral cavity squamous cell carcinoma. BMC Cancer. 2017;17(1):1–9.
67. Chen PCH, Pan CC, Kuo C, Lin CP. Risk of oral nonmalignant lesions associated with human papillomavirus infection, betel quid chewing, and cigarette smoking in Taiwan: an integrated molecular and epidemiologic study. Arch Pathol Lab Med. 2006;130(1):57–61.
68. Bascones-Martínez A, López-Durán M, Cano-Sánchez J, Sánchez-Verde L, Díez-Rodríguez A, Aguirre-Echebarría P, et al. Differences in the expression of five senescence markers in oral cancer, oral leukoplakia and control samples in humans. Oncol Lett. 2012;3(6):1319–25.

Hot Topics

Contents

Chapter 16 **Causal Inference in Oral Health Epidemiology – 267**
Gustavo G. Nascimento and Benjamin W. Chaffee

Chapter 17 **Socio-Economic Inequalities in Oral Health – 279**
Ankur Singh, Jose Leopoldo Ferreira Antunes, and Marco A. Peres

Chapter 18 **Life Course Oral Health Epidemiology – 295**
Marco A. Peres, Karen Glazer Peres, Flavio Fernando Demarco, Marcos Britto Correa, and Anja Heilmann

Chapter 19 **Sugar Consumption and Oral Health – 307**
Anja Heilmann, Carolina Machuca Vargas, and Richard G. Watt

Chapter 20 **Oral Health-Related Quality of Life – 319**
Georgios Tsakos and Finbarr Allen

Chapter 21 **Ecosocial Oral Health Epidemiology – 333**
Samuel Jorge Moysés and Ankur Singh

Chapter 22 **Use of Primary Care Settings to Collect Epidemiological Data – 347**
Gill Davies and Iain A. Pretty

Chapter 23 **Big Data and Machine Learning – 357**
Stefan Listl and Alexandre D. P. Chiavegatto Filho

Chapter 24 **Epigenetics in Oral Health – 367**
Toby Hughes

Chapter 25 **The Relationship Between Periodontal Diseases and Chronic Diseases – 379**
Fábio Renato Manzolli Leite and Gustavo Giacomelli Nascimento

Chapter 26 **Dental Health Services Epidemiology – 395**
David Brennan

Chapter 27 **Bioethics of Epidemiological Oral Health Studies – 409**
Jonathon Timothy Newton

Chapter 28 **Epidemiology, Politics, and Dental Public Health – 419**
Carol C. Guarnizo-Herreño, Paulo Frazão, and Paulo Capel Narvai

Chapter 29 **Water Fluoridation – 437**
Andrew John Spencer

Chapter 30 **Teaching Oral Epidemiology – 453**
Richard D. Holmes and Georgios Tsakos

Causal Inference in Oral Health Epidemiology

Gustavo G. Nascimento and Benjamin W. Chaffee

Contents

16.1 Introduction – 268

16.2 Historical Perspective – 268
16.2.1 Induction and Falsification – 268
16.2.2 Deterministic Causal Models: Necessary Causes and the Sufficient-Component Causes – 269
16.2.3 Probabilistic Causation and the Counterfactual Approach – 270

16.3 Statistical Versus Causal Association – 271

16.4 Causal Diagrams to Inform Stronger Analytic Designs – 272
16.4.1 Basic Components of Causal Diagrams – 272
16.4.2 Basic Principles of Causal Diagrams – 273

16.5 Randomized Experiments: The Only Option from Which to Infer Causality? – 275

16.6 Analytical Approaches for Causal Inference in Observational Data – 275
16.6.1 Marginal Structural Modeling – 275
16.6.2 Structural Equation Modeling – 276
16.6.3 Instrumental Variables – 276
16.6.4 Standardization and the Parametric G-Formula – 276

16.7 Conclusions – 277

References – 277

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_16

Learning Objectives

- To review the theories on causation in epidemiology
- To discuss the difference between statistical and causal associations
- To introduce the use of directed acyclic graphic in oral research
- To present the causal inference analytical approaches most used in oral research

16.1 Introduction

Humans have a natural inclination to explain the events and circumstances around us and to make predictions about future outcomes. Causal inference is a process of gathering information to make educated judgments about attribution. Causal questions seek to know not just how things are, but how things would change under a specific disruption to the state of the world. In oral health research, for instance, causal questions ask not how many people have periodontal disease or whether periodontal disease prevalence is higher among individuals with or without diabetes; rather, a causal question might ask whether improving an individual's metabolic condition will make periodontal disease less likely to occur. The latter question is more challenging. Drawing such insight demands application of external knowledge and assumptions that go beyond the data typically at hand. While more difficult to answer, the causal question also holds greater relevance for identifying what interventions or treatments will have the desired effect on disease occurrence.

As with epidemiology, generally, causal inference does not attempt to draw conclusions about the cause of health or illness for an individual patient. Instead, we seek insight into factors that drive disease rates at the population level. From another perspective, imagine a target population of interest with all variables sharing some joint distribution. There could be some parameter in this large population we might want to know, say, the prevalence of dental caries among all community-dwelling children of age 5 years. Our data could be a simple random sample of 5-year-old children from this target population. *Statistical inference* concerns how well the prevalence of dental caries in our sample approximates age-5 caries prevalence in the population. Metrics like confidence intervals help us evaluate the statistical precision of our estimate of that target parameter. *Causal inference* poses a more ambitious question. We ask what the joint distribution of variables would be in the population under some "intervention." Perhaps: how would age-5 caries prevalence change if all children had access to fluoridated water? In drawing causal inference, we rely on our sample data to estimate that causal target parameter. However, the data alone do not convey how distributions would be different under some intervention on the system: in this case, what caries prevalence would be under an alternate condition in which all children had accessed fluoridated water. Barring parallel universes [1], this alternate outcome is unobservable. To make causal inference from the observable data, we must make assumptions about the data-generating process, some of which cannot be verified.

Many of these sometimes unverifiable assumptions are already familiar to any student or practitioner of oral health epidemiology. We often assume that our sample data are representative of the target population; that "exposure" occurred before "outcome"; that observations are free of measurement error; and that no confounding remains after accounting for measured covariates. This chapter discusses these assumptions (and others) a bit more formally and in a causal inference context. Better causal inference demands that investigators be explicit about the parameters they wish to estimate and the assumptions inherent in their analyses, including assumed relationships between variables (measured and unmeasured). No spreadsheet or statistical software knows whether tooth brushing temporally preceded tooth decay or understands why flossing prevalence is so low among edentulous adults. What investigators bring to the analysis is outside knowledge, subject-matter expertise, and, above all, common sense.

16.2 Historical Perspective

16.2.1 Induction and Falsification

Causation has long been an essential concept in epidemiology. In the epidemiology literature, causal claims like "*smoking causes lung cancer*" have been made since the seminal US Surgeon General's report *Smoking and Health* (1964) [2], which was later expanded by Bradford Hill (1965) [3]. However, causal inference thinking was present at the onset of modern science, around the 16th and the 17th centuries, when a period of rapid expansion in new technologies coincided with a critical examination of the origins of knowledge. Since then, several theories have been formulated to define and explain causation. Although the objective of this chapter is not to review all the causal theories in depth, a brief overview of relevant theories to epidemiology will be provided at the risk of oversimplification. This overview of how causal thought has evolved may help to clarify current causal understanding in epidemiology.

Inductivism was the first attempt to more formally define and characterize causal thinking. According to

this theory, scientific reasoning was said to depend on generalizations, or inductions, from general laws of nature, which means that the observations are expected to induce the formulation of a natural law in the scientists' mind. This philosophy assumed that an event would in the future follow a similar pattern as it had in the past [4]. Despite the attempt at formulating a scientific thought, this theory carried no logical force. As a conclusion based on a set of observations may be wrong, even if the individual observations are true, inductivism fails to determine causal connections [5]. According to Hume, inductivism, at most, reports a series of events [6]. Regardless of its limitations to explain causation, such a theory was a great step forward from the medieval scholasticism, as instead of appealing to faith and humor, scientists were required to make careful observations of people and nature. In addition, inductivism has paved the way to the establishment of inferential criteria, which are still in use today [7].

The falsification or refutation philosophy encourages scientists to subject a newly formulated hypothesis to meticulous tests that may forge the hypothesis [8]. If a test refutes the hypothesis, a new hypothesis ought to be formulated and submitted to further tests. Therefore, the refutation theory defines an interminable cycle of new hypotheses and refutations. Such a school of thought stimulates scientists to elaborate on competing (alternative) hypotheses and to test them against one another. Thus, what is known as scientific literature is a body of unrefuted hypotheses that seem to explain existing observations, but that may be refined or even discarded. This theory also enables depersonalization of a hypothesis, as criticism does not necessarily imply criticism of the person who proposed it, but of the refuted hypothesis itself. The major vulnerability of this philosophy relies on the premise that refutations are hypothesis-based, and consequently, uncontrolled or unimagined biases in the refutation tests might invalidate our competing hypotheses. Furthermore, the requirement that all hypotheses are indefinitely and universally open to refutation fails to instill a sense of urgency for translating biological or epidemiologic work into disease prevention. Let us examine the following example about smoking and periodontitis:

Example of Falsification/Refutation

"Our current hypothesis indicates that smoking increases the risk of periodontitis onset and progression. However, like all other hypotheses, it could be proven false at any time."

That apparent equivocation is hardly an inspiration to quit smoking to prevent periodontitis, as refutation may be imminent. Although falsification theory still influences current causal thinking, the definition of causation goes further.

16.2.2 Deterministic Causal Models: Necessary Causes and the Sufficient-Component Causes

The idea that causes *affect* or *alter* outcomes has led to the concept of "one cause and one disease." While the monocausal theory has driven causal thinking for decades, highly influenced by development of microbiology, current knowledge recognizes that virtually all diseases have more than one cause. The acknowledgment of multifactorial diseases has demanded a differentiation between causes, which, conventionally, have been classified as either necessary or sufficient [9]. Sufficient causes comprise causes that, if present, will inevitably lead to disease, while necessary causes are considered essential to disease onset but may not cause disease in isolation [10].

Example of necessary and sufficient causes

HIV infection is a necessary (but not sufficient) cause of AIDS, while the presence of all or part of a third copy of chromosome 21 is sufficient (and necessary) to cause Down syndrome.

The most meticulous criteria for causes are that they are both sufficient and necessary. Most people would easily accept that exposure to a certain agent may not be sufficient to cause a given disease: not everyone who eats a lot of fermentable carbohydrates develops dental caries. However, it is harder to admit that a cause is only necessary when the very same cause is part of the disease definition, like in infectious or hereditary diseases. Chronic diseases, such as periodontitis and cardiovascular diseases, are characterized by a number of well-studied risk factors, which individually need not be necessary or sufficient. The lack of a priori knowledge about what can cause a disease, and the time lapse between a given exposure and its effect on health, preclude easy categorization of causes as necessary, unnecessary, or sufficient, but also reveal that we are likely unaware of all the possible causes underlying a certain disease [10].

In this context, Rothman has suggested the sufficient-component model, which incorporates the understanding that diseases have more than one single cause [11]. According to Rothman's model, also known as the causal pie model, the cause of any disease comprises a constellation of components (causes) that act together (inter-

act). The model also describes how causes can be either necessary, sufficient, both, or neither. A disease occurs when the necessary component causes are present as part of a complete constellation of causes. In addition, each constellation represents a sufficient set of component causes, and there may be more than one set of components capable of initiating disease. Although the true cause of a disease is the assemblage of sufficient components acting together, epidemiologists and public health professionals have often focused on few particular components, because their elimination or control would be enough to dismantle the entire causal mechanism. Advantages of the pie-model proposed by Rothman include (1) the multicausality; (2) the dependence of the strength of component causes on the distribution of complementary causes; and (3) the interaction between component causes.

The sufficient-component model, however, has some limitations that undermine its applicability as the ultimate definition of causation in epidemiology. The major criticism of this theory relates to its deterministic nature. To be considered necessary, the specific cause shall be present in all the constellations of causes; or there shall be only one particular constellation of causes in which no other sufficient causes are found. This definition includes causes that are not formally necessary, but demands that, within a certain set of conditions, all causes must be necessary and sufficient. At an individual level, as the occurrence (or nonoccurrence) of an event is determined by the existing conditions, all events are thus entirely deterministic. The issue with determinism is the difficulty in translating from abstract to reality. Scientists have rarely identified causes that present a "one to one" effect on the presumed outcomes. For example, although people with a high amount of dental biofilm are more inclined to develop periodontitis, biofilm is not by itself necessary or sufficient for periodontitis. The sufficient-component school of thought assumes that a biofilm is one component in a sufficient cause and that the other components have not yet been identified. In other words, this theory requires the assumption that uncountable, unknown components must be modified to transform a correlation into determinism [12]. Additionally, as many of the best-described epidemiologic risk factors are only weakly associated with their diseases at the population level, one must assume that the effect of the unknown causal components is much stronger than the effect of the known causes. Another limitation of this causal definition relates to its inability to capture a dynamic cause–effect model, that is, a dose–response relationship. While setting a series of sufficient causes, each with a different dose of the varying component cause, seems a solution for this problem, this approach fails to portray the smooth continuum of dose–response relations [13]. To solve the deterministic issue, a probabilistic (also known as "statistical") definition of causation has been formulated.

16.2.3 Probabilistic Causation and the Counterfactual Approach

Note

For a clear understanding of the counterfactual thinking, one may watch the movie "Sliding Doors." In this movie, the main character gets fired, and on her way to take her train, she misses it. From this scene beyond, the plot splits into two storylines, presented counterfactually, in which different events happen, consequent upon whether or not she catches her train.

The probabilistic causal definition posits that a cause increases the probability (or the chance) that its effect will manifest [14]. According to this understanding of causation, the occurrence of a disease (for instance, periodontitis) may be partially a matter of probability, reflecting in an indeterministic process. Hence, a probabilistic cause may be neither necessary nor sufficient for a given disease. However, a sufficient cause can be defined as a cause that raises the probability of its effect to 1, while a necessary cause merely increases probability from 0. The probabilistic definition of causation can be adapted to Rothman's sufficient-component causes [11]. Instead of being sufficient for an effect, components should instead contribute to the effect probability. Accordingly, the probabilistic theory circumvents the belief in uncountable unknown effects for every association. However, one may not assume that a cause increases each individual's risk by exactly the same amount: some people develop periodontitis in the presence of a heavy biofilm, while others do not, for instance. Accordingly, it becomes challenging to distinguish between a causal relationship and a noncausal association.

During the philosophical discussion about causality, one idea was constantly debated: a cause–effect relation could be understood as similar or slightly varying versions of reality. Hume firstly described causation in terms of the counterfactual in 1748 as "We may define a cause to be an object followed by another, and where all the objects, similar to the first, are followed by objects similar to the second. Or, in other words, where, if the first object had not been, the second never had existed." Even though the topic was intensively discussed, the topic remained obscure, and few scientists tried to use counterfactuals to explain causation. Only in 1973 did

counterfactuals reappear as a way to explain causation (see: Lewis [15]). For a formal definition of counterfactual causation, one must estimate the contrast between one outcome given certain conditions and another outcome given alternative conditions, had everything else remained constant. Although the counterfactual definition is insufficient to define causation by itself, it provides a conceptual framework that may enhance the distinction between causation and association. The counterfactual framework allows us to wonder: how would the state of the outcome (disease) change if it were possible to observe a world in which everything had taken place identically *except* for the presumptive cause (exposure)?

Point of Emphasis

Counterfactual Approach

If a patient had not smoked tobacco since adolescence, she would not have developed periodontitis in adulthood. While a helpful conceptional framework, one must carefully interpret counterfactual conclusions, because, without time travel, the counterfactual condition is not observable. In essence, the same individual cannot be observed as both a smoker and a never-smoker.

The pragmatic concept of causation, firstly introduced by Susser [16], defined a cause as "any factor, whether event, characteristic, or other definable entity, so long as it brings about change for better or worse in a health condition." However, some epidemiologists argue that *intervention* must be included as part of the definition of causation, often discussed in the context of randomized control trials (RCTs) or hypothetical interventions [17]. Promoters of a broader (pragmatic) understanding of causation claim that this model embraces the concept of multiple causes, and argue that the adoption of a restrictive approach would reduce significantly the field of epidemiology [18]. On the other hand, proponents of an interventionist definition of causality argue that causal claims should be made on the basis of well-specified interventions, that is, "human-made" interventions. According to these authors, the inclusion of nonmodifiable attributes of individuals (e.g., sex, race) as potential causes would lead to vague questions: in particular, how to conceptualize the counterfactual for an immutable state of being. Nevertheless, one has to bear in mind that while some causes are not modifiable by human interventions, others are not modifiable yet (e.g., genetic manipulation).

To solve the dispute between the pragmatic and the interventionist definitions of causation, a pragmatic pluralistic approach of causality and causal inference has been claimed in epidemiology. Such an approach recognizes that there are different ways of thinking causality, and epidemiologists should use the approach that seems more adequate to address their epidemiologic questions of interest. According to Vandenbroucke et al., "pragmatic pluralism is a combination of quietism about the nature of causation, and pluralism about the causal concepts" [19]. Thus, while the interventionist approach of causation is of particular use when designing a public policy or intervention, the pragmatic pluralistic notion is often used to identify an etiology or a problem to solve [20].

16.3 Statistical Versus Causal Association

Let us examine the following scenario: in a certain population, if a given event occurs with a frequency of f_1 and another event occurs with a frequency of f_2, it is possible to assume that the proportion of people with a combination of both events will be $f_1 \times f_2$, given that both events occur independently. If f_1 is a determinant of a disease, and f_2 is a disease, some persons in this population will develop a disease (f_2) in the presence of the determinant f_1 only as a matter of coincidence. However, if this scenario is either greater or smaller than just an agreed level of coincidence, one may conclude that the conditions are statistically associated.

Epidemiological studies have been roughly categorized into descriptive, explanatory, or predictive studies. Irrespective of the relevance of descriptive studies, explanatory and predictive studies have been the ones considered in our attempts to infer causality. Although causality is not certain in explanatory and prediction studies, association is presumably a prerequisite for even posing a causal question.

In research, statistical association has been accepted as a relevant tool. Scientists are encouraged to formulate a hypothesis a priori, and then to test their hypothesis statistically in contrast to an alternative hypothesis (also called as null-hypothesis), in line with the falsification theory. The scientific method uses deductive logic to infer predictions from explicit hypotheses and compares observations with those predictions. There are many advantages in using this approach to identify potential causes. The presence of an underlying theoretical framework informs the research question and gives weight to the observations that emerge. Additionally, the use of explicit theoretical principles allows researchers to criticize each other's assumptions objectively, a central tenet of scientific research, because even seemingly flawless assumptions may not be "true."

Statistical association is often considered in prediction studies. Contrary to explanatory studies, prediction studies do not require a theoretical framework, as they do not intend to explain a condition. In epidemiology,

prediction studies are often able to anticipate trends and outcomes. In public health, these studies are valuable tools to identify and target individuals at a high risk of having or developing a certain disease. Prediction studies can be also used to estimate probabilities of a diagnosis or a prognosis outcome, especially in the clinical setting. In oral health, prediction models have been developed for diseases such as dental caries [21] and periodontitis [22].

Irrespective of the importance of statistical association in explanatory and predictive studies, causality should not be inferred from statistical association alone. Several issues may be raised on the use of statistical methods as the only source for determining causal relationships. For instance, the limited number of individuals in some studies affects the statistical power of a given test and, therefore, increases the chance of failing to reject the null hypothesis, even when it is false. Additionally, in explanatory studies, the lack of a clear hypothesis, demonstrated through an explicit conceptual framework to formalize basic causal perceptions, may lead to spurious statistical associations. A great example to illustrate how statistical associations may be misleading when drawing causal conclusions was published by Hujoel et al. [23]. In this article, the authors found a strong association between dental flossing and obesity, two causally unrelated conditions. Thus, according to the authors, application of simplistic epidemiologic methodology based exclusively on statistical associations is inappropriate for inferring causality.

As the use of purely statistical association fails to properly identify causal associations, other criteria should be examined. The development of considerations (or conditions) to adjudicate a series of potential causes implies an inductive process to verify specific assumptions. Bradford Hill proposed the following "viewpoints" (often misleadingly referred to as "criteria") to consider in assessing whether an association is causal: (1) strength; (2) consistency; (3) specificity; (4) temporality; (5) biologic gradient; (6) plausibility; (7) coherence; (8) experimental evidence; and (9) analogy [3]. Hill recognized the relevance of many factors in decision-making that go beyond a set of rules and statistical significance. For this reason, instead of naming them criteria, Hill presented his viewpoints as considerations, saying, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non." The importance of each of the nine viewpoints has been debated over time. Other than temporality, as it is indisputable that a cause must come before its effect, there is no strict criterion for determining whether an association is causal or not. According to Rothman: "universal and objective causal criteria, if they exist, have yet to be identified" [7].

16

16.4 Causal Diagrams to Inform Stronger Analytic Designs

Causal diagrams, also known as directed acyclic graphs (DAGs), provide a framework for encoding assumptions about causal and noncausal relationships between variables. By following a set of notations and "rules" governing how the graphs are drawn and interpreted, investigators unlock a powerful tool to inform appropriate analytic plans. In particular, the diagrams can be used to identify relationships, such as confounding, selection bias, mediation, and others.

Causal diagrams derive from earlier work in computer science [24] that was adapted for use in epidemiology [25, 26]. Multiple citations review their application in various topics across medicine and the social sciences [27, 28], including oral health [29, 30]. This chapter does not attempt to review all nuances, theoretical backing, and potential uses of causal diagrams, but does strive to explain basic principles as primer for further reading and exploration.

To understand how causal diagrams might help researchers avoid common pitfalls in analysis, consider two examples to which we return later:

1. Dr. Kahnyne recently finished data collection on a large longitudinal study of dental health, nutrition, and socioenvironmental factors. Dr. Kahnyne performs separate chi-square tests with his outcome variable, carious decay into dentin, and each of the 74 other variables in the dataset. He then fits a logistic regression for the outcome (visually evident decay) that includes all variables that were associated with tooth decay in the chi-square tests at a selected threshold ($P < 0.20$).
2. Dr. Denton is a supporter of increasing access to fluoride for children in her community. A city official is concerned that providing fluoride might result in caregivers allowing their children to eat more sugary foods. The official's reasoning is that caregivers will be lenient about sugary snacks if they believe that their fluoride-treated children are protected against tooth decay [31]. Dr. Denton examines the data from all 6-year-old children in the city. She wants to adjust for confounding, so she runs a logistic regression model for the outcome sugar consumption, with fluoride treatment, socioeconomic position, and caries status as independent variables.

16.4.1 Basic Components of Causal Diagrams

- *Nodes* refer to the variables shown on the graph, usually drawn from left to right in temporal order, but the spatial distance between them is rarely

Fig. 16.1 In this relatively simple causal diagram, tobacco smoking is a cause of tooth loss, and socio-economic position is a shared cause (ancestor) of both. Each variable is shown as a node with arrows indicating assumed causal relationships along the edges between nodes

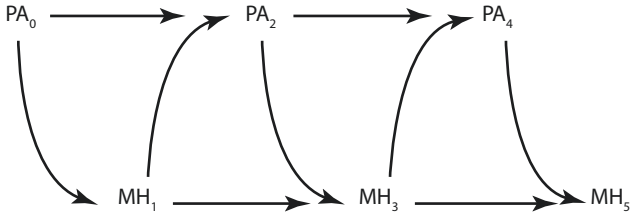


Fig. 16.2 Nodes at multiple time-points can convey changes over time and indicate feedback loops while maintaining an acyclic structure. Here, physical activity at time zero (PA_0) is an ancestor of mental health at time one (MH_1), which in turn, is an ancestor of later physical activity (PA_2), and so forth

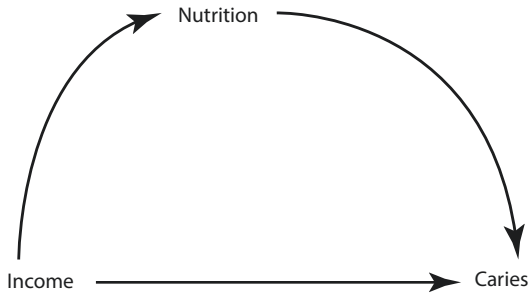


Fig. 16.3 Directed paths (all edges in the same direction between exposure and outcome) can be direct (single edge) or indirect (passing through a mediator). Here, nutrition is a proposed mediator between monetary income and dental caries. Income also has a direct effect on caries not mediated by nutrition (this direct effect itself could be mediated by other variables not shown in the diagram)

meaningful. Frequently, variables are abbreviated as a single letter (for instance, "*Y*" for the designated outcome variable; "*L*" for a time-varying longitudinal covariable), but this convention varies.

- *Edges* are lines connecting the nodes. The absence of an edge implies no causal link between variables. All edges are marked with arrows in one direction: from cause to effect (hence, *directed* acyclic graphs). Regardless of whether the presumed causal effect is positive or negative (inverse), the arrowed edges are drawn identically.
- *Parents* (or ancestors) and *descendants* refer to nodes that are causes and effects, respectively, in relation to each other. In Fig. 16.1, socioeconomic position and tobacco smoking are both ancestors of tooth loss. Tobacco smoking is a descendant of socioeconomic position.

16.4.2 Basic Principles of Causal Diagrams

- Causal diagrams are *acyclic* (hence, directed *acyclic* graphs). Bidirectional relationships and feedback loops can be conveyed by showing events unfold over time (Fig. 16.2).
- Nodes can represent variables that are measured and quantifiable, as well as variables that are conceptual, unknown, or *unmeasured*.
- A *path* is a sequence of consecutive edges. A *direct path* is a single edge that connects two nodes with no node between, whereas an *indirect path* is a directed path (all edges in the same direction) that includes one or more intermediate nodes (Fig. 16.3). Indirect paths indicate mediation.
- A *backdoor path* is a type of nondirected path (all edges not in the same direction) that indicates confounding. In Fig. 16.1, if the main causal path of interest is from the exposure tobacco smoking to the outcome tooth loss, there is a backdoor path from tobacco smoking to tooth loss via socioeconomic position. A shared ancestor of both exposure and outcome, in this diagram, socioeconomic position, is a confounder of the smoking–tooth loss relationship.
- Paths can be *open* or *blocked*. A directed or backdoor path is blocked when *conditioning* on a node along the path. In this context, conditioning usually refers to statistical adjustment, such as through stratification or multivariable adjustment, as would be done to account for a confounding variable in data analysis. A rectangle is drawn around the conditioned node. Confounding has been fully taken into account when there are no open backdoor paths from exposure to outcome (Fig. 16.4).
- A *collider* is a node where edges from opposite directions meet (Fig. 16.4). A collider also blocks a path. However, conditioning on a collider reopens a path otherwise blocked at the collider.
- Directed acyclic graphs often encode *selection bias*, as in the case of conditioning on a collider. Selection into the study population, for example, by virtue of inclusion/exclusion criteria or by retention in a cohort (i.e., not lost to follow-up), can be represented as a node. Because analysis is restricted to the analytic sample, there is conditioning on the selection

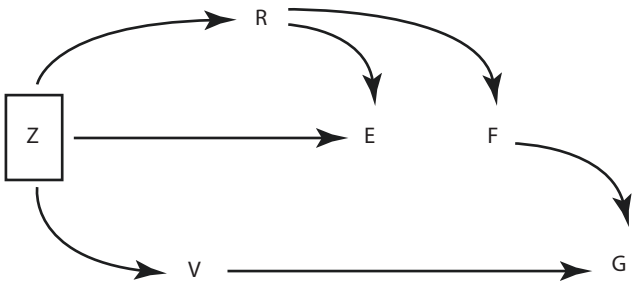


Fig. 16.4 This diagram assumes that gender (Z) is potential cause of taking vitamins (V), exercising at the gym (E), and making New Years' resolutions (R). Making resolutions is also a cause of exercising and flossing (F), which in turn, is a cause of gingivitis (G, remember: causes can be protective). Thus, there is a backdoor path from vitamins to gingivitis through gender, resolutions, and flossing than can be closed by conditioning on any of these variables. However, the path from vitamins to gingivitis passing through exercise is blocked at the collider (E)

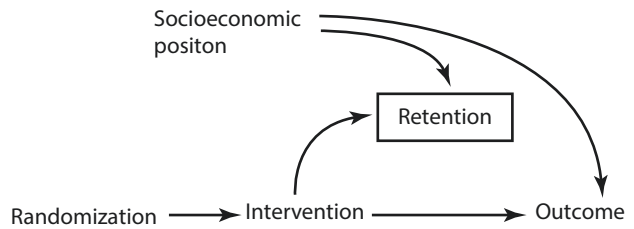


Fig. 16.5 Conditioning on a collider opens a path that would have been blocked. In this randomized control trial, retention is affected both by being in the intervention group (unpleasant side effects, perhaps) and socioeconomic position. However, socioeconomic position is also a potential cause of the outcome. By necessity, analysis is restricted to those who finished the trial, but this form of conditioning opens a path through retention; thus, losses to follow-up can result in selection bias

node (Fig. 16.5). If there are open paths from both the exposure and outcome of interest to the selection node, this conditioning will open a path through the collider, inducing a noncausal association between exposure and outcome in the data (See: Box – Example of collider bias).

With these principles in mind, creating a causal diagram prior to conducting data analysis may clarify whether a variable is a mediator, confounder, or collider. However, the expected relationships between variables depend on how the causal diagram is drawn (Fig. 16.6). Where to draw the nodes and how to set the paths between them depends on subject matter knowledge and assumptions from the investigators, particularly when there is legitimate scientific uncertainty regarding the nature of the underlying causal relationships. Figure 16.6 is based on a published example [29] that shows how causal diagrams encode assumptions that inform how statistical associations are interpreted.

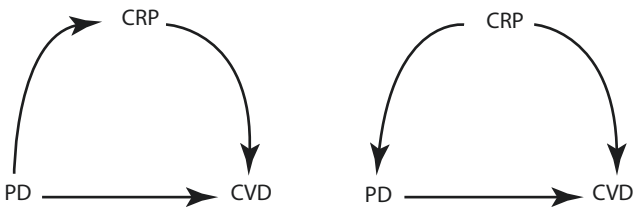


Fig. 16.6 How to interpret observed associations in data depends on assumptions than can be encoded in causal diagrams. Left: C-reactive protein (CRP) is a mediator along a causal path from periodontal disease (PD) to cardiovascular disease (CVD). Right: CRP sits on a backdoor path as a shared parent of both periodontal disease and cardiovascular disease. Figure reused from Merchant & Pitiphat [29] with permission from John Wiley and Sons

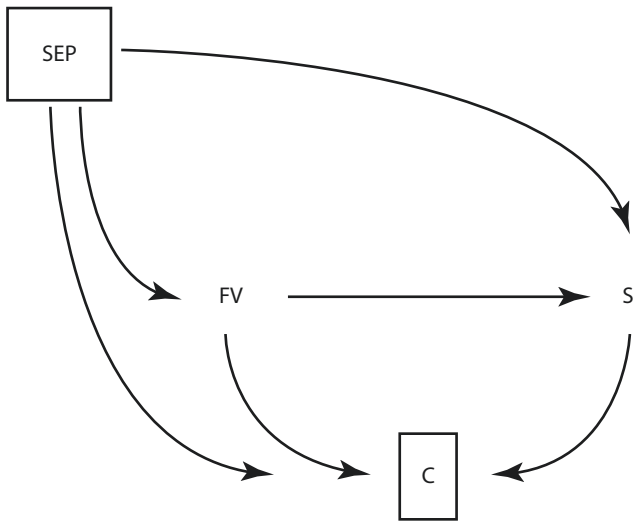


Fig. 16.7 The hypothetical Dr. Denton adjusted her estimate of the association between fluoride varnish (FV) and sugar consumption (S) for caries status and socioeconomic position (SEP). Based on this diagram, caries is a collider, and conditioning on it will bias the association between fluoride and sugar away from the underlying causal effect

Returning to earlier examples, Dr. Kahnyne (of the 74 possible covariables) designed an analysis plan that was systematic and reproducible but also not informed by subject matter expertise. Relying on p-values from a preliminary round of pair-wise hypothesis testing as the only arbiter of what variables were maintained in the multivariable model, Dr. Kahnyne marched forward without consideration of whether included variables were confounders, colliders, or mediators.

Figure 16.7 shows one plausible interpretation Dr. Denton's investigation into whether the security of fluoride coverage encourages reckless junk food consumption. The hypothesis to test is shown as the direct path from fluoride to sugar intake. Reasonable assumptions are that fluoride and sugar are ancestors of caries (whether protective or risk factors, the paths are drawn identically). Therefore, caries status is a collider; includ-

ing it in the regression model would affect the observed association between fluoride and sugar intake, biasing it away from the underlying causal relationship Dr. Denton had hoped to measure.

Causal diagrams are often more complex than the examples given in this chapter. Using the same set of tools, potential sources of bias, including nonadherence, time-dependent confounding, measurement error, and others can be expressed. There are limitations, as well. In practice, the graphs do not convey the magnitude of causal effects. Also, there is no easy convention for conveying effect modification, in which the nature of the relationship between one pair of variables differs depending on the context, such as the presence or absence of a third variable. Despite these restrictions, causal diagrams are a remarkably accessible shared language to inform analytic strategies and convey underlying assumptions. The increasing use of directed acyclic graphs in oral health epidemiology is a welcome development for strengthening causal inference.

Point of Emphasis

Collider Bias

Imagine an airline with an unusual way of determining who gets first class seats. At the gate, the airline computer assigns first class seats completely randomly. The gate agent then gives any luckily selected passenger a purple hat as a signal to the flight attendant to seat the passenger in first class (again, it is a usual business model). There is another way to get into first class: once onboard, a passenger can answer a riddle from the flight attendant that only the cleverest people can solve. Remember, hats were assigned randomly (independent of cleverness). No causal link exists between being clever and getting (or not getting) a purple hat. However, *conditional* on being seated in first class, whether someone has a hat conveys information about cleverness: in first class with no hat = must be clever. To re-*cap*, err, review... getting a purple hat causes being in first class; being clever causes being in first class; first class is a collider (shared consequence of two otherwise unrelated variables); conditional on the collider (being in first class), there is an induced statistical association between hats and cleverness that does not exist for the airplane overall (unconditional on seat class).

16.5 Randomized Experiments: The Only Option from Which to Infer Causality?

Randomized control trials (RCTs) have long been considered the "gold standard" in causal inference. Randomization assures that individuals are assigned only by chance to either the experimental or the control (no intervention) group. Random allocation of the intervention prevents confounding, because the distribution of all factors that might potentially influence the outcome will be evenly distributed between groups. Assuming a sufficiently large study population, it can be assumed that both groups (intervention and control) are comparable in their characteristics, and thus, exchangeable. Exchangeability implies that the effect of the intervention would have been the same in both groups, in that the intervention group is a good approximation of what the control group would have experienced under the intervention had group assignment been reversed (and vice versa).

Although randomized experiments are highly informative, randomized trials are not an option in many situations. In the quest to infer causality, one has to bear in mind that it is not possible to intervene in all conditions (some conditions are not modifiable) and other conditions cannot be assigned (it is not possible to randomize premature birth, for instance). Furthermore, random assignment to interventions with adverse outcomes raises serious ethical concerns. For instance, researchers cannot assign a person to smoke cigarettes or receive an unnecessary organ transplant. In addition to ethical considerations, economic aspects also limit the feasibility of an RCT. Randomized experiments can be expensive to conduct, because they often involve extensive human resources and material costs. Due to their high costs, RCTs are often sponsored by private companies, and on this occasion, conflict interests may exist.

16.6 Analytical Approaches for Causal Inference in Observational Data

Causal inference approaches to observational data were first widely adopted in the social sciences and economics. These methods have been more recently adopted by epidemiologists, with a constantly growing literature on this topic. The literature covering methodologic techniques available to draw causal evidence from observation data is too vast to review in depth. Instead, we briefly present selected analytical approaches often used in dental research at the risk of some oversimplification.

16.6.1 Marginal Structural Modeling

Marginal structural modeling (MSM) is a class of causal models that estimate, from observational studies, the effect of a given exposure at the population level (i.e., marginally). Advantageously, MSMs can distinguish between confounders and mediators (variable that simultaneously influences the outcome and is influenced by the exposure). Hence, MSMs reduce the chance of collider bias and fill a gap left by conventional

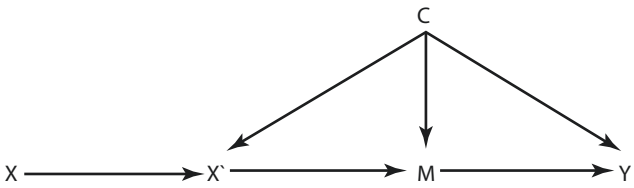


Fig. 16.8 Conceptual framework of the study conducted by Krishna Rao (2015) on the effect of childhood socioeconomic disadvantage on oral cancer in adulthood. X: Exposure – Childhood socioeconomic condition; X`: Adulthood socioeconomic condition; M: Mediator – Smoking/Chewing Tobacco/Alcohol; Y: Outcome – Oral Cancer; C: Confounders – Age and Sex. Figure was adapted and reused with the permission from Wolters Kluwer Health, Inc

regression methods to assess mediation. The parameters of an MSM can be consistently estimated using stabilized inverse-probability-of-treatment weights (IPW), which allows inclusion of time-varying exposures in the presence of time-varying covariates. Under MSM assumptions, causation can be inferred from association.

Although MSMs have been widely used in epidemiology since first proposed by Robins et al. (2000) [32], the approach has been used less often in oral health research. One example that depicts the use of an MSM in dental research is the relationship between prolonged breastfeeding (24 months or beyond) and dental caries. Using MSM and accounting for confounders and mediators, Chaffee et al. [33] found that prolonged breastfeeding increased the risk of severe early childhood caries. These findings were further corroborated by Peres et al. [34], who also used MSM to investigate this relationship.

Krishna Rao and colleagues [35] also used an MSM to estimate the effect of childhood socioeconomic disadvantage on oral cancer. After controlling for confounders and mediators (tobacco and alcohol), the authors concluded that early life socioeconomic condition had an effect on oral cancer in adulthood. Figure 16.8 depicts the direct acyclic graph with the conceptual framework of the study.

16.6.2 Structural Equation Modeling

Structural equation modeling (SEM) is a class of causal modeling that is often used to assess unobservable latent constructs, which are estimated based on a set of observed variables. In addition to the use of latent variables, SEM allows the assessment of complex causal relationships between one or more dependent and independent variables, and accounts for mediation without introducing collider bias. For these characteristics, SEM has been commonly used in the social sciences. In dental research, SEM has been often used to investigate relationships that include latent constructs, such as quality of life [36] and oral health behaviors [37]. More recently, it has been proposed that SEM could be used in dental research to describe multidimensional conditions, like periodontitis [38, 39].

For example, an application of the SEM approach was related to investigating the relationship between metabolic syndrome and periodontitis [39]. In this study, the authors used factor variables to describe both metabolic syndrome and periodontitis. The findings of this study indicated that metabolic syndrome influenced severe, but not mild periodontitis. Additionally, when both metabolic syndrome and periodontitis were treated as observed variables, no association was found. One limitation of the SEM approach relates to estimates originated from this analysis, as coefficients may be more difficult to interpret for policy makers and health professionals than other well-known measures, such as risk ratios.

16.6.3 Instrumental Variables

This approach considers random variation in a variable (called an "instrument") that influences the exposure but is not causally associated with the outcome or any unobserved confounders. The instrument variable may not be directly related to the outcome, but only indirectly via the exposure variable. Instrumental variable analysis overcomes residual confounding due to unmeasured confounders, and thus, it is a useful approach in economics, social sciences, and epidemiology.

In a study evaluating the relationship between socioeconomic condition and tooth loss after the 2011 Great East Japan Earthquake, Matsuyama et al. [40] used the distance of participants' residence from the coastline as the instrumental variable. This distance was a powerful predictor of house destruction and loss of wealth. The authors found that economic deterioration and housing damage impacted tooth loss, and therefore, suggested a causal relationship between these conditions (Fig. 16.9).

16.6.4 Standardization and the Parametric G-Formula

Standardization involves the calculation of an expected number of events that are then compared to the number of observed events. In a given population, the marginal risks for the exposed and unexposed individuals are estimated as the weighted average of risks across the strata of each covariate (confounder or mediator) with weights equal to the proportion of individuals in each stratum of each covariate. Although standardization appears as an alternative to IPW, the methods are based on different modeling assumptions.

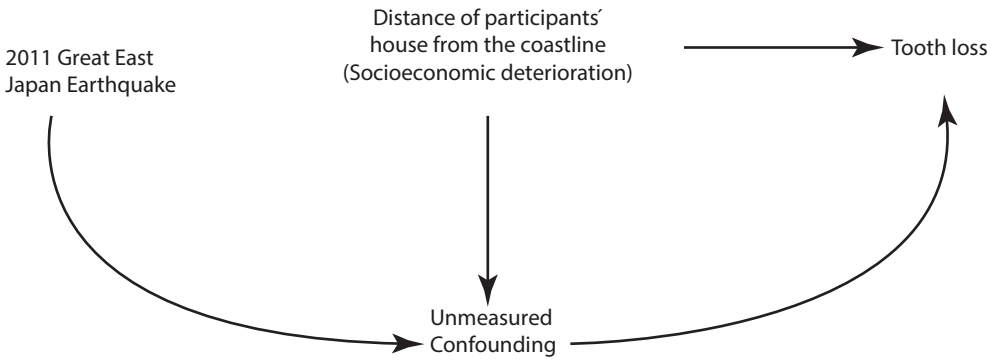


Fig. 16.9 Use of instrumental variable (distance of participant´s house from the coastline) to estimate the effect of economic deterioration on tooth loss after the 2011 Great East Japan Earthquake. Based on Matsuyama et al. [40]

G-formula, a broad term to describe approaches that rely on standardization, is of particular use in epidemiology as it properly accounts for repeated measures of explanatory variables at several points in time. Additionally, this approach can be used to estimate the population risk of a disease under hypothetical scenarios, and therefore, provides useful information for health professionals and policy makers. However, estimates originated from this approach should not be extrapolated to other populations with different distribution of covariates, because the g-formula standardizes the risk to the distribution of covariates according to the population under investigation.

In dental research, this approach was used to estimate the hypothetical effects of health detrimental conditions (smoking, alcohol, and diet) combined with obesity on the risk of periodontitis. According to the authors' findings, the combination of obesity with unhealthy behaviors increased the risk of periodontitis [41].

16.7 Conclusions

Causal inference yields evidence that can inform public health interventions and clinical practice to prevent disease, improve health, and potentially, enhance health equity. Importantly, however, there are meaningful questions in oral health epidemiology that do not require causal evidence. Descriptive data that reveal temporal trends, quantify the population burden of disease, and characterize oral health disparities are tremendously valuable for planning resource allocation and setting research priorities. Beyond quantifying effectiveness, public health actions should also be assessed for efficiency and acceptability: essential elements for sustainability. Statistical associations, particularly those that are predictive, even if not causal, can be highly informative. For example, in caries risk assessment, a clinician may note a patient's dental insurance or health benefit status. Eligibility for public benefits is certainly not a cause of dental caries, but to the extent the measure predicts caries risk, preventive treatment can be tailored accordingly.

Regardless of analytical methodology, inference, whether statistical or causal, relies on the plausibility of the underlying assumptions and the quality of the available data. A complex statistical tool is poor compensation for deficiencies in study design, whether sampling bias, measurement error, or incomplete data. Investigators can greatly enhance the strength of their causal evidence well before data analysis by following best practices in study planning and data collection.

The proliferation of causal thinking in oral health epidemiology has inspired interest in parameters that better align with plausible public health interventions. Several analytical approaches have been developed to estimate these parameters from data, including propensity score matching, g-computation, inverse weighting, and other estimators. Yet, above and beyond these advances in data analysis, one of the most powerful contributions of causal thinking has been to motivate epidemiologic investigators to be more explicit and transparent regarding the rationale and assumptions underlying their methodological approach. Causal diagrams are one tool for expressing some of these assumptions.

No matter the care taken, it is highly unlikely that all assumptions will be true. It is near impossible that "all" confounding factors could be adequately measured and taken into account in any observational study, for example. Interpretation of causal evidence remains a question of subjective judgment and reasoning, no matter how sophisticated the statistical modeling. This uncertainty invites reflection on Bradford-Hill's eloquently stated causal considerations, as a process of qualitatively weighing the evidence across multiple lines of inquiry for consistency, temporality, and plausibility.

References

1. Gott JR III. Creation of open universes from de Sitter space. Nature. 1982;295(5847):304.
2. E. United States Department of Health, and Welfare, Smoking and Health. Report of the advisory committee to the Surgeon General of the Public Health Service. Washington, D.C.: Government Print Office; 1964.

3. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
4. Mill JSA. System of logic, ratiocinative and inductive. 5th ed. London: Parker, Son and Bowin; 1862.
5. Russel B. A history of western philosophy. New York: Simon and Schuster; 1945.
6. Hume D. A treatise of human nature. Oxford: Oxford University Press; 1888.
7. Rothman K, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
8. Popper KR. Logik der Forschung. Vienna: Julius Springer; 1934.
9. Parascandola M, Weed DL. Causation in epidemiology. J Epidemiol Community Health. 2001;55(12):905–12.
10. Scheutz F, Poulsen S. Determining causation in epidemiology. Community Dent Oral Epidemiol. 1999;27(3):161–70.
11. Rothman KJ. Causes. Am J Epidemiol. 1976;104(6):587–92.
12. Mayr E. Cause and effect in biology. Science. 1961;134(3489):1501–6.
13. Hogan MD, Kupper LL, Most BM, Haseman JK. Alternatives to Rothman's approach for assessing synergism (or antagonism) in cohort studies. Am J Epidemiol. 1978;108(1):60–7.
14. Olsen J. Some consequences of adopting a conditional deterministic causal model in epidemiology. Eur J Pub Health. 1993;3:204–9.
15. Lewis D. Counerfactuals. Oxford: Blackwell; 1973.
16. Susser M. Judgement and causal inference: criteria in epidemiologic studies. Am J Epidemiol. 1977;105(1):1–15.
17. Hernan MA. Invited commentary: hypothetical interventions to define causal effects--afterthought or prerequisite? Am J Epidemiol. 2005;162(7):618–20; discussion 621-2.
18. Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiol. 1991;133(7):635–48.
19. Vandenbroucke JP, Broadbent A, Pearce N. Causality and causal inference in epidemiology: the need for a pluralistic approach. Int J Epidemiol. 2016;45(6):1776–86.
20. Glymour C, Glymour MR. Commentary: race and sex are causes. Epidemiology. 2014;25(4):488–90.
21. Disney JA, Graves RC, Stamm JW, Bohannan HM, Abernathy JR, Zack DD. The University of North Carolina Caries Risk Assessment study: further developments in caries risk prediction. Community Dent Oral Epidemiol. 1992;20(2):64–75.
22. Du M, Bo T, Kapellas K, Peres MA. Prediction models for the incidence and progression of periodontitis: a systematic review. J Clin Periodontol. 2018;45(12):1408–20.
23. Hujoel PP, Cunha-Cruz J, Kressin NR. Spurious associations in oral epidemiological research: the case of dental flossing and obesity. J Clin Periodontol. 2006;33(8):520–3.
24. Pearl J. Probabilistic reasoning in intelligent systems: networks of plausible inference. San Francisco: Morgan Kaufmann Publishers Inc; 1988.
25. Robins J. A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. J Chronic Dis. 1987;40(Suppl 2):139S–61S.
26. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37–48.
27. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8:70.
28. Howards PP, Schisterman EF, Poole C, Kaufman JS, Weinberg CR. "Toward a clearer definition of confounding" revisited with directed acyclic graphs. Am J Epidemiol. 2012;176(6):506–11.
29. Merchant AT, Pitiphat W. Directed acyclic graphs (DAGs): an aid to assess confounding in dental research. Community Dent Oral Epidemiol. 2002;30(6):399–404.
30. Akinkugbe AA, Sharma S, Ohrbach R, Slade GD, Poole C. Directed acyclic graphs for oral disease research. J Dent Res. 2016;95(8):853–9.
31. Hedlund J. Risky business: safety regulations, risks compensation, and individual behavior. Inj Prev. 2000;6(2):82–90.
32. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550–60.
33. Chaffee BW, Feldens CA, Vitolo MR. Association of long-duration breastfeeding and dental caries estimated with marginal structural models. Ann Epidemiol. 2014;24(6):448–54.
34. Peres KG, Nascimento GG, Peres MA, Mittinty MN, Demarco FF, Santos IS, Matijasevich A, Barros AJD. Impact of prolonged breastfeeding on dental caries: a population-based birth cohort study. Pediatrics. 2017;140(1):e20162943.
35. Krishna Rao S, Mejia GC, Roberts-Thomson K, Logan RM, Kamath V, Kulkarni M, Mittinty MN. Estimating the effect of childhood socioeconomic disadvantage on oral cancer in India using marginal structural models. Epidemiology. 2015;26(4):509–17.
36. Gururatana O, Baker SR, Robinson PG. Determinants of children's oral-health-related quality of life over time. Community Dent Oral Epidemiol. 2014;42(3):206–15.
37. Mizutani S, Ekuni D, Tomofuji T, Irie K, Azuma T, Iwasaki Y, Morita M. Structural equation modeling to assess gender differences in the relationship between psychological symptoms and dental visits after dental check-ups for university students. Acta Odontol Scand. 2015;73(5):368–74.
38. Rebelo MA, de Castro PH, Rebelo Vieira JM, Robinson PG, Vettore MV. Low social position, periodontal disease, and poor oral health-related quality of life in adults with systemic arterial hypertension. J Periodontol. 2016;87(12):1379–87.
39. Nascimento GG, Leite FRM, Peres KG, Demarco FF, Correa MB, Peres MA. Metabolic syndrome and periodontitis: a structural equation modeling approach. J Periodontol. 2018;90:655.
40. Matsuyama Y, Aida J, Tsuboya T, Hikichi H, Kondo K, Kawachi I, Osaka K. Are lowered socioeconomic circumstances causally related to tooth loss? A natural experiment involving the 2011 great East Japan earthquake. Am J Epidemiol. 2017;186(1):54–62.
41. Nascimento GG, Peres MA, Mittinty MN, Peres KG, Do LG, Horta BL, Gigante DP, Correa MB, Demarco FF. Diet-induced overweight and obesity and periodontitis risk: an application of the parametric G-formula in the 1982 Pelotas Birth Cohort. Am J Epidemiol. 2017;185(6):442–51.

Socio-Economic Inequalities in Oral Health

Ankur Singh, Jose Leopoldo Ferreira Antunes, and Marco A. Peres

Contents

17.1 Introduction – 280

17.2 Key Motivations for Investigating Oral Health Inequalities – 281

17.3 Theoretical Explanations for Socio-Economic Inequalities in Oral Health – 282

17.4 Operationalisation of Theoretical Explanations for Socio-Economic Inequalities in Oral Health – 284

17.5 Measurement of Socio-Economic Inequalities in Oral Health – 284

17.5.1 Different Types of Measures of Social Inequality – 284
17.5.2 Levels of Aggregation – 285
17.5.3 Composite Measures of Socio-Economic Inequalities in Oral Health – 286
17.5.4 Measurement of Socio-Economic Inequalities in Oral Health: Scale of Measurement – 287

17.6 Advancements – 288

17.6.1 Intersectionality Theory – 288
17.6.2 Causal Inference and the Potential Outcome Approach – 288
17.6.3 Decomposition of Socio-Economic Inequalities in Oral Health – 289
17.6.4 Simulation Modelling – 289

17.7 Way Forward and Conclusion – 289

References – 290

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_17

Learning Objectives

After reading this chapter you will be able to:

- Identify reasons why examining socio-economic inequalities in oral health is important
- Understand theoretical explanations for socio-economic inequalities in oral health
- Recognise different methodological aspects of examining socio-economic inequalities in oral health
- Identify opportunities in recent developments in epidemiology that can enhance current understanding of socio-economic inequalities in oral health

17.1 Introduction

More socially advantaged people and societies are reported to have better health outcomes and life expectancy than their disadvantaged counterparts, almost universally. Oral health outcomes do not differ from other health outcomes in this regard. Systematic reviews have confirmed associations between socio-economic disadvantage and oral health outcomes of dental caries, dental care utilisation, oral cancer, tooth loss and traumatic dental injuries, periodontal disease and poor quality of life [1–11]. Individual studies have confirmed socio-economic inequalities in oral health outcomes in both high as well as low- and middle-income countries [12–16]. When socio-economic inequalities in oral health outcomes are compared with general health outcomes within a country, often inequalities in oral health outcomes are more pronounced than those in general health outcomes [17, 18]. Studies that have examined trends in oral health inequalities over time have also confirmed that improvements in oral health outcomes have not been consistent across socio-economic groups [13, 19–21]. Majority of the research on socio-economic inequalities in oral health is descriptive, reporting associations between one or more measures of socio-economic disadvantage and oral health outcomes at the national and sub-national level. This body of evidence has helped establish the extent and nature of oral health inequalities across societies and the persistent and pervasive nature of socio-economic inequalities in oral health [22]. However, it also places onus on oral health researchers and advocates to have an improved understanding of the causes of oral health inequalities with the motive to find solutions that can address this societal challenge.

Several shifts have acted as fulcrum points for the change in the theoretical understanding of oral health inequalities and potential solutions. Major ones include the shift from attention to determinants of oral health at the individual level to those at the population level [23, 24], from biomedical aetiological models of oral diseases to a social determinants model of disease aetiology [22, 25], and the failings of individually oriented behavioural change strategies [26], paving ways to interventions targeting environments and placing lesser responsibility on already disadvantaged individuals. Achievements in the theoretical understanding of oral health inequalities are to be supported with robust and actionable evidence from oral epidemiological investigations to help policymakers make evidence-informed decisions on solutions to address oral health inequalities. Often, equity impacts of public health interventions are not studied, and even well-intended interventions (media campaigns, workplace smoking bans) can increase socio-economic inequalities in health outcomes [27]. Therefore, oral epidemiologists have a vital role to play in checking and confirming such popular assumptions.

It is now widely recognised in oral epidemiology that socio-economic determinants of oral health exist beyond the control of individuals. This is substantiated by increased application of the multilevel analytical framework and its corresponding techniques [28]. Traditionally, randomised controlled trials have dominated as the most reliable source of evidence for the effectiveness of public health interventions. However, large-scale trials with sufficient follow-up are next to impossible with many social exposures as they are determined politically (e.g. changes in income distribution as an intervention). In epidemiology and social epidemiology, there is increased utilisation of observational data by using methods based on potential outcome approaches to estimate and inform the causal effects of exposures onto health outcomes [29]. However, their application has been relatively limited in oral epidemiology, mainly to explain the relationship between socio-economic disadvantage and oral health outcomes. There is also a greater emphasis on the need for conducting more ‘consequential’ research that leads to inform specific interventions for improving population health [30]. Epidemiology is also witnessing an interesting intersection of methods from data science such as machine learning for better prediction of exposure groups [31] and computational simulation models [32] that provide unique opportunities to understand better the potential of public health interventions in reducing the population burden of diseases as well as associated inequalities. The shift mentioned above in theoretical thinking related to the understanding of drivers of oral health inequalities at the population level needs to be occurring similarly in oral epidemiological studies of oral health inequalities, without neglecting the fundamental concepts related to investigations on social inequalities in health.

In this chapter, we discuss important methodological aspects related to investigating socio-economic inequalities in oral health. Core methodological aspects, along with some recent developments in the social epidemiology will be highlighted, keeping in mind their relevance to operationalisation in oral health research. Additionally, social epidemiology and the studies of socio-economic inequalities in health are plagued with terminologies that are overlapping but have different meanings. Often, naively there has been interchangeable use of these terminologies (e.g. health inequalities, health inequities, health disparities; social position, socio-economic position, social class and social status) in health research. Although they may generally refer to a similar phenomenon, they involve different underlying theories, whose interchangeable use often masks nuances of definition. New researchers to health inequalities research and students may find this daunting to grasp and difficult in circumventing this issue. Readers will be directed in this section towards some useful glossaries that they may find helpful for avoiding such practices. Measurement of oral health inequalities requires attention to scales on which they are measured [33]. Discussion on different scales of measurement is critical as policy responses to address oral health inequalities are likely to be different based on the choice of scales [34]. Additionally, we discuss some of the main social and epidemiological theories advanced to explain why and how social inequalities in oral health occur.

Certain caveats of this chapter must be highlighted to the readers. In this chapter, we have not attempted to review the extent and magnitude of socio-economic inequalities in every oral health outcome. We opted to provide a general theoretical overview along with a stronger emphasis on the methodological issues related to oral health inequalities research. Additionally, due to the evolving nature of research on social inequalities in health, readers are advised to use the presented material more as a platform to enhance their understanding of research on socio-economic inequalities in oral health rather than as a definitive set of rules to follow.

17.2 Key Motivations for Investigating Oral Health Inequalities

The World Health Organization defines health inequalities as the differences in health status, or in the distribution of health determinants, between different population groups [35]. Gene expressions and constitutional variations among individuals can result in variations in health status within populations. Due to the ageing process, with increasing age people may have relatively worse health outcomes than their younger counterparts. For example, the prevalence of periodontal disease is negligible among children and adolescents. Consequently, periodontal disease varies according to age-groups within populations. However, variations in health outcomes according to social disadvantage (social inequalities in health) have three distinguishing features that separate them from variations in health according to other characteristics. They are systematic, socially produced (hence modifiable) and unfair. Despite differences in magnitude and extent of inequalities, social patterning in health outcomes is universal. Therefore, they are intrinsically systematic. Second, health differences of this nature are not produced biologically but rather are a consequence of social processes. Therefore, social inequalities in health can be addressed by altering the underlying social processes. Finally, social inequalities in health are unjust and unfair [36].

The case for understanding and addressing social inequalities in health (and oral health) is profound. Social epidemiology as a discipline strives to understand how social interactions and purposive human activity affect health. Innumerable past and present social arrangements that exist within societies lead to differential exposures and differences in health status between individuals that comprise a population. The Nobel Prize winner and developmental economist Amartya Sen argues that 'in any discussion of social equity and justice, illness and health must figure as a major concern'. He justifies his arguments using a social justice framework. Health equity should be a central feature of the justice of social arrangements. Being healthy allows human capabilities to flourish as they get free from escapable illness, avoidable afflictions and premature mortality. Under this notion, it is serious injustice to preclude some individuals from these opportunities due to the inadequate social arrangements. Of note, illnesses that are not prevented and go untreated for social reasons such as lack of resources, rather than out of personal choice, have a particularly negative implication to social justice [37].

Despite being largely preventable, oral diseases continue to affect individuals due to social reasons. Socially disadvantaged people suffer a double burden because they face significant challenges concerning preventive and routine dental care in addition to already established social inequalities expressed in major oral health risk factors including tobacco use, unhealthy diet and oral hygiene in societies [38–44]. Epidemiological research on social inequalities in oral health is vital to document the extent of social inequalities in oral health within and between societies [13]. For example, it allows assessing whether social inequalities in oral health within a population has increased or decreased over

time. Comparisons in social inequalities in oral health between population groups are also essential to understand the underlying social, economic and political reasons due to which one population may have lower social inequality in oral health than another [45–47]. Other motivations may include identifying social groups that are most vulnerable to poor oral health, and strategies may be adopted to scale existing policies to reduce the high levels of disease within specific population subgroups [48, 49]. Equity impacts of health policies are equally important as is their ability to lead to reductions in overall rates of diseases. Surveillance activities to track and monitor oral health inequalities play a central role in generating hypotheses on the effectiveness of oral health policies and healthcare arrangements in reducing oral health inequalities. Oral epidemiology also has a central role in providing a better understanding of causal pathways through which social disadvantage leads to specific poor oral health outcomes [50, 51]. A better understanding of causal pathways is fundamental to the development of policies and strategies to reduce existing and future levels of oral health inequalities within and between societies.

17.3 Theoretical Explanations for Socio-Economic Inequalities in Oral Health

Theoretical explanations for explaining socio-economic inequalities in oral health have a crucial role to play in determining the potential of interventions in reducing inequalities. Therefore, substantial debates in the discipline of epidemiology and social epidemiology have emerged on the relevance of theoretical pathways. Although outstanding records of historical discussions on the relationship between different forms of social disadvantage and health were reported historically in works of Edwin Chadwick, Rudolf Virchow, John Snow and Frederick Engels, formal theories for the relationship between social inequality and health were only first reviewed in the Black Report [52].

Four theoretical categories were proposed to explain socio-economic inequalities in health in the Black Report – artefact; theories of natural or social selection; materialist or structuralist explanations and behavioural/cultural explanations [52, 53].

Artefact: The artefact explanations explain inequalities in health as a construct of the measurement process. It posits that the association between social position and health is a statistical artefact, which is a consequence of how social status has been classified or measured over time [52]. The fact that social inequalities in health outcomes, including oral health outcomes, have been presented with so many different markers of social disadvantage over time raises severe doubts on the validity of the Artefact category [54].

Theories of Natural or Social Selection: This theory is based on the premise of reverse causation – health leads to social disadvantage and not the other way around [52]. This theory can also be refuted on the basis that large number of longitudinal studies [55, 56], including birth cohort studies [57–59], establish that prior exposure to social disadvantage leads to poor health outcomes in future [54].

The two theoretical categories (artefact and natural/social selection) do not hypothesise how social disadvantage leads to poor health outcomes or the causal relationship between social disadvantage and poor health outcomes. On the contrary, materialist or structuralist explanations and behavioural/cultural explanations provide causal hypotheses on how social disadvantage may lead to poor health outcomes.

Materialist or Structuralist Explanations: The materialist explanation places importance on the role of economic and socio-structural factors in the distribution of health and well-being. This line of explanation for variations in health status is consistent with the radical Marxian critique of the direct impact of economic conditions on health outcomes. Variations in rates of mortality are attributed to exploitation and poverty. The theoretical framework stresses the role of material deprivation in the social production of disease. The materialist explanation is contested because variations in health status are still observed in societies that have achieved high levels of economic development. Material deprivation and labour exploitation in such societies are minimal due to trade-union organisations and wage council machinery. A counter-argument to this limitation is that in countries that have achieved high levels of economic development, relative rather than absolute deprivation in terms of health resources and material circumstances are more relevant. Consequently, relative deprivation leads to variations in health status according to social positions [52].

Behavioural/Cultural Explanations: A behavioural/cultural approach is based upon the independent and autonomous causal role of health behaviours in morbidity and mortality. One version of this theoretical approach values individuals as a unit of analysis. Consequently, this approach stresses lifestyle and irresponsible behaviour of individuals among certain social groups as the reasons for poorer health. The underlying reasons for such behaviour include lack of education, knowledge and attitude towards healthy behaviour.

Another more theoretically developed version relates to the 'culture of poverty' hypothesis. This approach considers the process of biological and social adaptation at lower levels of social position leading to a structure of norms, ideas and behaviours. This culture develops integrity and stability over time due to its role in helping individuals cope with their environments and impacts on their socialisation practices, and therefore, on their health behaviours [52].

Theories of social epidemiology, including materialist/structural and behavioural/cultural explanations, are grounded in social relations and systematic distribution and misallocation of social resources relevant to health.

A psychosocial theory focusing on the role of constant stress arising from feelings of lack of control and relative disadvantage among individuals lower in the social hierarchy to those who are more advantaged in the aetiology of poor health outcomes is also postulated [41, 43, 50, 60].

The Black Report concluded that choosing between these complex and competing theoretical approaches may be difficult; whereas the authors believe that the best answer lies in the materialist explanations [52]. The theoretical approaches discussed in the Black Report have been both used to explain health inequalities (differences in health among social groups within a society) as well as differences in average health of societies according to their level of social inequality (studies of social ecology) [53]. However, some specific theories/theoretical approaches aim only to explain the relationship between social inequality and average health status at the levels of different geopolitical units [53]. These theoretical explanations are synthesised below.

1. Materialist: The materialist explanations stress the role of environmental factors on health, which tend to vary according to the degree of income inequality of society. Macroeconomic factors such as unemployment and levels of economic development lead to hazardous work and living environments that lead to poorer health on average [61].
2. Behavioural: The behavioural explanations state that more unequal societies produce more unhealthy behaviours compared to equal societies. This fact is either due to individual inadequacies and/or due to the presence of social gradients in health behaviours [61].
3. Psychosocial: At an individual level, the psychosocial explanation claims that inequality impacts on health in two different ways. First, people's perception of their position in the social hierarchy affects health. Second, lack of control and lower levels of social hierarchy leads to persistent stress that can physiologically lead to poor health or health-damaging behaviours that consequently lead to poorer health. Compared to an equal society, in a more unequal society, there is a higher degree of social evaluative threats (comparisons between people). When added to the lack of control and coping strategies, it leads to higher levels of persistent stress. Therefore, a more significant decrement in power and control across the social hierarchy in more unequal societies leads to poorer health on average [53, 62–64].
4. Social Capital: Social capital explanations branch out from the psychosocial explanation as this theory posits that an unequal distribution in income undermines trust and damages social relationships at a population level [65]. The lack of trust and social support are the critical reasons for poorer population health in unequal societies [66].
5. Neo-Material: In contrast to the psychosocial and the social capital theories, the neo-material theory posits that more unequal societies tend to have a cluster of lack of material resources and systematic underinvestment in social infrastructure, such as public policies in health, which leads to poorer health at a population level [67–69].

Among the different theoretical explanations, a significant debate in social epidemiology persists about the relevance of psychosocial and social capital pathways in comparison to the neo-material pathway to explain the negative impact of social inequality on population health [53, 62–64, 67–71]. An underlying sociological distinction between the two positions is that while the psychosocial and social capital pathways originate from a Durkheimian perspective on collective consciousness and social integration, the neo-material pathway stems from Marxist or rational choice orientation [65]. Due to the difference in the origin of the theories, a conceptual challenge also relates to the interpretation of what aspects of social inequality does income inequality capture that is related to poor health or higher mortality rates at the population level. Those supporting the neo-material pathway identify income inequality as a product of structural socio-political determinants such as the dominant political paradigm, the welfare state, social class relations, including exploitation due to unequal distribution of production resources. On the other hand, supporters of psychosocial and social capital pathways identify income inequality as an operational measure of social stratification and hierarchy. They argue that the detrimental impacts of income inequality are related to a higher degree of social stratification. A high degree of social stratification in unequal societies results in loss of trust, social support and social cohesion. Through jealousy, it leads to adverse psychological impacts on individuals across the social hierarchy.

17.4 Operationalisation of Theoretical Explanations for Socio-Economic Inequalities in Oral Health

Sisson [50] reviewed the application of theoretical explanations for social inequalities in health, particularly in the context of oral health. Four theoretical explanations (materialist, cultural/behavioural, psychosocial and life-course perspective) were discussed.

Concerning the materialist explanation, lack of access to dental services, low purchasing power for a healthy diet and lack of access to fluoridated water due to social disadvantage were identified as primary forms of material disadvantage.

Despite the criticism of behavioural/cultural explanations for social inequalities in health in the Black Report itself, interventions for improving oral health at the population level have been directed mainly to changing individual health behaviours [26]. Studies from Australia and the US have confirmed that adjustment of oral health behaviours could not explain observed socio-economic inequalities in oral health outcomes [39, 41, 43].

Studies that tested psychosocial factors (psychological distress, allostatic load and cognitive ability) as explanations for oral health inequalities found limited support [42, 60, 72].

Oral health presents all requisites to adopt a life-course framework. Most oral diseases and disorders of public health importance are relatively common, they are cumulative and chronic, take time to develop and are mostly preventable. Different theories are proposed to explain how harmful and beneficial exposures to ill-health over the lifespan act. Programming or critical period effect states that exposure occurring during the crucial developmental period leads to a condition later in life. The critical period with effect modifier postulates that critical early-life exposures interact with later ones. The accumulation of risk models proposes that detrimental and beneficial exposures accumulated through life, affect health and finally, the chain of risk model states that one exposure leads in a reasonably linear way to another to influence health later in life [73].

Evidence on life-course theory in oral health is available from very few population-based birth cohorts which included dental/oral health clinical assessments over time. Notably, The Dunedin Multidisciplinary Health and Development Study, which started in 1972 in New Zealand and 1982, 1993, 2005 and 2015 Pelotas (Brazil) birth cohort studies are still active. The Dunedin Study used a mix of socio-economic indicators to assess socio-economic position at cohort participants in childhood. Dental plaque, gingival bleeding, periodontal diseases and decayed surfaces at aged 26 were negatively associated with childhood socio-economic status. As socio-economic status increased, the amount of poor oral health indicators decreased even after controlling for childhood health and adult socio-economic status. Moreover, low adult socio-economic status had a significant effect on poor adult dental health after controlling for low childhood socio-economic status [57].

Findings from the 1982 Pelotas birth cohort studies showed that poverty over at least one stage of life had harmful effects on adolescent's (aged 15) dental caries, oral health-related behaviours and dental service usage. Upwardly mobile income between childhood and adolescence improved dental care [59]. At 24 years of age, the study findings showed that poverty experience in early life was associated with unsound teeth. Moreover, the number of episodes of poverty over life increased the prevalence of unsound teeth [74]. Later on, at the age of 31 years, Schuch et al. showed that adults belonging to low and fluctuating income trajectories from childhood to adulthood had twice as much the prevalence of periodontitis than participants with stable high-income trajectories [75]. The direct effect of early in life occurrences of poverty on periodontitis in adulthood was also reported [56]. On the other hand, in the 2004 Pelotas birth cohort study, differences in income trajectories from childhood to young adulthood were associated with the management of dental caries-treated and untreated rather than in the experience of the disease [76].

A scoping review examined evidence on the application of theories in the relationship between area-level social inequality and population oral health outcomes [51]. Authors noted that psychosocial theories were the most used. Although studies often mentioned theories, the majority of selected studies did not test any theory. Therefore, there is a need for explicit testing of theoretical explanations for oral health inequalities.

17.5 Measurement of Socio-Economic Inequalities in Oral Health

17.5.1 Different Types of Measures of Social Inequality

Conceptual clarity on *what* socioeconomic parameters must be measured and *why* is vital for monitoring and understanding socio-economic inequalities in oral health [77]. Of critical importance is the difference between social class, socio-economic position and socio-economic status as they continuously appear and are

mistakenly used interchangeably in studies on social inequalities in (oral) health.

Social class refers to groups originating from relationships that are economical and are determined by a society's forms of property, ownership, labour and dependencies through production, distribution and consumption of goods, services and information. It is not an 'a priori' property of individual human beings, but it is an outcome of a social relationship created by societies [77]. Of significant value is the importance of power and exploitation in the class relationships where resource owners gain economically from non-owners. Therefore, the relational aspect of social class distinguishes it from the stratification-based approaches. For more information on applied measures of social class, check the references (78–83). Several studies have applied social class measures in oral health literature [84–87].

Socio-economic position is an aggregate concept that comprises of both resource-based and prestige-based measures and relates to both childhood and adulthood social position. Resource-based measures are material and social resources and assets such as income, wealth and education. While prestige-based measures reflect an individual's rank in a social hierarchy, referring to people's access to and consumption of goods, services and knowledge as an outcome of their occupational prestige, income and education [77]. A good description of measures of socio-economic position, including advantages, disadvantages and relevance at different life-stages is described in the cited glossary [88]. Several reviews have summarised evidence on these socio-economic measures and oral health outcome(s) [3, 11, 55, 89, 90].

A study on German and Swedish adults reported low correlations between education, income and occupational class and reported a varying magnitude of associations between each of the measures and outcomes of diabetes, mortality and morbidity due to myocardial infarction and all-cause mortality [91]. It is usual in epidemiological research to mutually adjust for another measure of social position when estimating the causal association between one measure and a health outcome, for example, adjusting for education or occupation when examining the association between income and oral health. However, careful consideration is needed because the effect of education on health can be both direct and mediated through occupation and income. Similarly, the effect of occupation can be both direct and mediated via income but confounded by education. Finally, the effect of income can be confounded by occupation and income [92]. Clarity on the inter-relationships between social exposures and their roles as mediators, confounding factors and effect measure modification is key to assessing social inequalities in oral health and remove systematic sources of bias.

17.5.2 Levels of Aggregation

17.5.2.1 Socio-Economic Variations in Oral Health Between Populations

Majority of studies on socio-economic inequalities in oral health examine variations in oral health outcomes within a population according to a measure of social position (e.g., variations in dental caries according to educational attainment within Australia or test association between education and oral health outcome within Australia). Mainly, these are attributes of individuals or households. Alternatively, one can examine variations in oral health between populations. Populations and societies differ in their socio-economic characteristics. For instance, countries have differences in average income, distribution of income, proportion educated, level of social development and so on. Variations in oral health outcomes are confirmed according to country-level socio-economic characteristics [93–96]. At the sub-national level, studies have reported associations between area-level social disadvantage and oral health outcomes [97–104]. The reasons why variations in oral health outcomes must be examined between populations were described in detail previously [28]. The main reasons are as follows: there is growing evidence on the independent contribution of contexts in shaping oral health; variations in population oral health reveal underlying societal determinants; oral health determinants have a socio-political and multilevel nature; individual-level studies have a limited explanatory potential for population oral health; and finally, the need of informing strategies for prevention of oral diseases.

17.5.2.2 Fallacies Arising due to Misspecification of Variables or Level

Four different types of fallacies (ecological, atomistic, sociologistic and psychologistic) can occur due to either measurement issues or when the variable(s) from other levels of social organisation are ignored. An ecological fallacy can occur when associations between individual-level socio-economic exposure (e.g., individual-level income) and oral health outcomes are inferred from the observed associations at the group level (ecologic exposures (e.g., area-level mean income) and aggregate outcomes). Alternatively, if an association between ecologic exposures (e.g., area-level mean income) and aggregate outcomes is inferred from observed associations between individual-level socio-economic exposure (e.g., individual-level income) and oral health outcomes then it is a case of atomistic fallacy. The other types of fallacies, the sociologistic and psychologistic, may occur when the variable(s) from other levels of social organ-

isation are ignored. The sociologistic fallacy occurs when the role of individual-level factors (confounding, effect modification and mediation) is ignored in the group-level associations. Alternatively, psychologistic fallacy may occur when the role of group-level is ignored in the individual-level associations [28].

There are two main reasons for the use of area-level measures of socio-economic position. First, when there is a lack of individual-level data on socio-economic position, area-level socio-economic measures may be used as proxies. However, the individual-level socio-economic position often varies among areas and, therefore, using area-based measures can be misleading. When individual-level inferences are drawn from such studies, then the ecological fallacy cannot be ruled out [105, 106]. Second, area-level measures must be used when the socio-economic status of the context is the ecologic exposure of interest. Aggregated measures of socio-economic position have meanings that cannot be attributed to individuals, for example, income inequality is a measure of the distribution of income within a population and cannot be measured in an individual. A large volume of evidence in epidemiology [69] as well as in oral health [51] has examined income inequality as exposure of interest. In this case, measures of social disadvantage at the area level are treated as independent exposures rather than proxies for individual socio-economic disadvantage. Hence, the use of area-level socio-economic exposures must be theoretically supported. In addition to conceptual clarity and theoretical relevance of an area-level socio-economic exposure, several methodological aspects related to operationalising their research must be considered (types of cross-level associations, meaningful population groups, scale and unique characteristics, power and sample size, role of lag times and confounding by measures at alternate level of social organisation) [28].

17.5.2.3 Analytical Approaches

Ecological analysis and multilevel modelling are two main analytical approaches when dealing with area-level socio-economic exposures and oral health outcomes. In ecological analysis, associations are tested between group-level exposures (e.g. area-level mean income, area-level income inequality and the proportion of adults with university education) and aggregated oral health outcomes (e.g. proportion of adults with tooth loss, oral cancer notification rates). The ecological analysis is valuable for hypothesis generation and for examining variations in aggregated oral health outcomes according to policies implemented at group level [94–96, 107, 108]. However, they have many limitations among which ecological fallacy is critical. Additionally, the ecological analysis uses data generated only at one level (group level).

Multilevel modelling has many benefits as it utilises data across multiple levels of social organisation. First, inter-individual variations in oral health outcomes can be partitioned at different levels of social organisation to quantify how much context matters. Then, the contribution of specific group-level socio-economic exposures (e.g., area-level mean income, area-level income inequality, the proportion of adults with university education) in area- and individual-level variations in oral health outcomes can be quantified. Finally, associations between specific group-level socio-economic exposures and oral health outcomes of interest can be tested accounting for both group- and individual-level covariates simultaneously. Therefore, providing the opportunity to comprehensively examine the relationship between area-level socio-economic exposures and oral health outcomes [28, 109–112]. Multilevel modelling has been adopted with enthusiasm in oral health literature [110, 112–120]. However, most multilevel analyses in oral epidemiology is cross-sectional where the temporal order between exposure and outcome cannot be established.

17.5.3 Composite Measures of Socio-Economic Inequalities in Oral Health

For comparisons between populations and within populations over time, socio- economic inequalities in oral health outcomes can be estimated using composite or summary measures of inequality as they provide a common reference point for comparisons. Different types of measures are described below [33]:

1. *The Rate Ratio of Lowest* versus *Highest Socio-Economic Group*: The two groups must not be so extreme that composite measures ignore the majority of health inequalities and are sensitive to the idiosyncrasies of the two groups. However, they should also not be broad that composite measures do not reflect the extent of inequalities [33].
2. *The Rate Difference of Lowest* versus *Highest Socio-Economic Group*: Compared to rate ratio, this measure is the difference in health status between the lowest and highest socio-economic group [33].
3. *Regression-Based Relative Effect Index*: A regression model is fitted whereby morbidity and mortality rates are regressed onto socio-economic measures. The measures for the socio-economic position must be on an interval scale [33].
4. *Regression-Based Absolute Effect Index*: Untransformed morbidity and mortality rates are regressed onto continuous measures of socio-economic exposures [33].
5. *Population-Attributable Risk (Relative)*: This is the proportional reduction in overall morbidity and

mortality rates occurring when hypothetically everyone experiences the rates of the highest socio-economic group. It is estimated as the difference between the overall rate and the rate for the highest socio-economic group [33].

6. *Population-Attributable Risk (Absolute)*: The absolute population-attributable risk is obtained by multiplying population attributable risk with the overall rate.
7. *Regression-Based Population-Attributable Risk (Relative)*: First, the *regression-based relative effect index* is estimated. The *population-attributable risk* is estimated from the predicted rate estimated for the highest socio-economic group [33].
8. *Regression-Based Population-Attributable Risk (Absolute)*: This is obtained by multiplying by the morbidity or mortality rate in the whole population [33].
9. *Index of Dissimilarity:* This index shows the percentage of all cases that should be redistributed to obtain a similar rate of morbidity and mortality for all socio-economic groups [33].
10. *Relative Index of Inequality:* The relative index of inequality takes into account both the population size and the relative socio-economic position of groups. For its calculation, the morbidity and mortality rates of socio-economic groups are regressed onto the proportion of the population having a higher position in the social hierarchy. The estimated relative index of inequality can be interpreted as the ratio of morbidity/mortality rates of those at the bottom to those at the top of the hierarchy on the basis of association between morbidity/mortality and socio-economic position for all groups [33].
11. *Slope Index of Inequality:* This measure is the absolute analogue of the slope index of inequality. Inequality is presented as rate differences rather than rate ratios [33]. It represents the linear regression coefficient showing association between level of health in each socio-economic category and the ranking of socio-economic category on the social scale [121].
12. *Concentration Index:* This index is based on a 'concentration curve' where the x-axis is the cumulative proportion of people by their socio-economic position starting with those lowest and finishing with those highest and the y-axis represents the cumulative total proportion of health in these people. It ranges from −1 to 1; if all health was concentrated at the highest socio-economic position, then the concentration index will be 1 and vice-versa [121].
13. *Symmetrized Theil Index:* A Symmetrized Theil Index is the average of Theil Index and Mean Log Deviation (widely used measures of income inequality (a measure of divergence)). [122].
14. *Gini Index:* The Gini Index is based on the Lorenz curve, where the x-axis represents the cumulative proportion of people by health status as ranked in increasing order and the y-axis represents the cumulative total proportion of health of individuals [121].

Several examples exist on the application of composite measures of inequality in oral health outcomes [17, 103, 123–126].

17.5.4 Measurement of Socio-Economic Inequalities in Oral Health: Scale of Measurement

When presenting socio-economic inequalities in oral health, the scales on which they are presented are of critical importance – particularly, in cases where inequality is to be compared over time. Variations in oral health outcomes between socio-economic groups can be quantified both on absolute (difference) and relative (ratio) scales. The choice between absolute and relative measures of inequality is an important consideration given the fact that progress in reducing inequalities in one scale may not apply to the other.

Harper et al. [127] reported a case in which inequality increased overtime on a relative scale and decreased overtime on an absolute scale for the same context. Celeste and Fritzell [128] examined socio-economic inequalities in oral health outcome in Sweden within a population that was followed up for 43 years. Authors found different results on the absolute and relative scale. While relative inequalities were highest earlier in life and then decreased, absolute inequalities showed an increase up to middle adulthood, and then only marginally declined. When socio-economic inequalities were compared between European countries according to their welfare typology using measures of Relative Index of Inequality and Slope Index of Inequality, again, different groups of countries emerged as problematic on the absolute as well as the relative scale of inequality [46]. Therefore, it is possible in certain situations to see a reduction in inequality on one scale and not another. In such cases, some authors preferentially may select to report inequalities on a chosen scale with favourable results providing partial or incorrect evidence. Relying exclusively on one scale of measurement rather than the other can be misleading and may not provide the complete picture of progress in the reduction of inequalities [33, 34, 129]. Ways to plot both absolute and relative inequalities over time simultaneously have also been developed and can be used for communicating the scale of inequalities comprehensively [129].

The choice of scale to assess inequalities is also relevant when the study outcomes have two bounds; e.g. attainments, as being free of caries and shortfalls, as disease manifestation. In such cases, Kjellsson et al. [130] proposed assessing inequalities using attainment-relative, absolute and shortfall-relative measures, thus avoiding the suspicion that a perspective was chosen to favour some premise.

17.6 Advancements

In this section, we present recent advancements in the field of epidemiology and social epidemiology that provide unique opportunities to improve current knowledge on the understanding of socio-economic inequalities in oral health.

17.6.1 Intersectionality Theory

Theoretical advancements in social epidemiology endorse clarifying the roles of intersection between multiple forms of social disadvantage *(intersectionality)* in determining health and health inequalities [131]. How one form of socio-economic position may interact with other forms of social advantage (or disadvantage) in determining oral health outcomes is not well understood. Despite knowing that social exposures and identities such as gender, ethnicity, age, education, disability, indigenous status and income are shaped by societal systems of oppression and privilege [131, 132], studies treat these measures as independent to each other concerning health. Such exercise risks considering these exposures as measures of individual risk and ignores the intersection between different forms of social identities [133]. Therefore, there is a compelling argument to apply an intersectionality framework to examine interlocking between income and other social exposures when studying the determinants of oral health and oral health inequalities [131, 132].

One way to deal with intersectionality is to test interactions between different forms of social disadvantage. However, large sample sizes with sufficient statistical power are necessary for this purpose. Multilevel regression models [28] are demonstrated to address this issue and quantify the effect of intersection between social identities in determining health status [132, 133]. Random intercepts for all possible combinations of categories of multiple exposures are fitted, and each socio-economic exposure is also included in the same model to explain variation in health status between different 'intersections' of social advantage and social disadvantage. The remaining variation in health status after including all social exposures in fixed part signifies the total interactive effect of multiple social exposures. Predicted estimates from multilevel models can also help profile intersectional strata according to their risk or advantage in oral health. Otherwise, when the role of other forms of social disadvantage in the relationship between income and oral health outcomes is studied through modelling interaction or effect modification, it must be assessed and reported appropriately on both additive and multiplicative scales [134].

17.6.2 Causal Inference and the Potential Outcome Approach

Typically, randomised controlled trials were considered as the only source of any causal evidence on the effect of an intervention on an outcome. However, they are often not possible with social exposures. Additionally, most randomised controlled trials have small follow-up periods where the life-course effects of social exposures are impossible to be studied. Instead, there is a surge in the development and application of statistical and epidemiological techniques that are based on the 'potential outcome approach' framework and allow for examining causal effects with observational data. By emulating randomised controlled trials in their operation, achieving exchangeability between the exposed and non-exposed, these methods are able to quantify total causal effects under strong assumptions. Examples include the estimation of causal effects of social disadvantage on health [135] or modelling utility of interventions in reducing existing socio-economic inequalities in health [136]. Also, the total causal effect can be further decomposed into natural indirect effect, the proportion of effect transmitted through measured pathways and the natural direct effect, the proportion of effect transmitted through other possible pathways by mediation analysis. This form of mediation analysis has several advantages over traditional methods such as allowing for interactions between exposure and mediators and accounting for the exposure-induced mediator outcome confounding.

It is of paramount importance that oral epidemiologists capitalise this opportunity. First, theoretical pathways through which social disadvantage lead to oral health outcomes can be quantified and better understood through causal mediation analysis. An excellent example is how sequential causal mediation analysis is applied to quantify causal effect of disability acquisition on mental health and further decomposed into material, psychosocial and behavioural pathways [137]. Policy interventions as mediators can also be set to a specific value to simulate their effectiveness in reducing oral

health inequalities through estimation of the controlled direct effects [138]. It must be noted that causal modelling approaches have strong assumptions of no confounding among others. Therefore, theoretically informed directed acyclic graphs and clarity on exposure definitions will be the foundation of any causal investigation between socio-economic disadvantage and oral health outcomes [139]. Selection bias and information bias leading to differential or nondifferential misclassification of socio-economic exposure and oral health outcomes must be carefully considered as they reduce confidence in causal estimates.

17.6.3 Decomposition of Socio-Economic Inequalities in Oral Health

Once health inequalities are estimated, the next step is to find explanations for the observed inequalities. Decomposing health inequalities into the factors that contribute to it can achieve this. A decomposition method was implemented by Blinder and Oaxaca (Oaxaca-Blinder decomposition technique) [140, 141], which has also been applied to decompose health inequalities into contributing factors [142, 143]. In this technique, the outcome gap between two groups is divided in a component due to differences in magnitudes of determinants of the outcome between groups and another component that is attributable to group differences in the effects of these determinants. Recently, this method has been applied in oral health to quantify the contribution of modifiable factors to area-level socio-economic inequalities in oral health in Australia [144]. It has also been applied to examine the contribution of the municipal Human Development Index in estimated mean differences in indicators of the public dental services between fluoridated and non-fluoridated municipalities in Brazil [107]. Similarly, the decomposition technique has been used to assess the contribution of demographic and socio-economic factors to oral health inequalities over time within and between Canada and the USA [145].

17.6.4 Simulation Modelling

Policymakers are often faced with the difficulty of making policy decisions within finite resources and political windows of opportunity. Comparisons across public health interventions in terms of their overall population health impacts as well as equity impacts are therefore necessary to make informed decisions. Programs of research that quantify health impacts of interventions (example: Assessing Cost-Effectiveness (ACE)-Prevention study) [146] allow for such comparisons, both among interventions targeting a specific risk factor and also across different health interventions. Computer simulation models help quantify the potential impact of public health interventions. Evidence confirms their application in tobacco control [147, 148], human papillomavirus (HPV) vaccination [149], dietary interventions [150], colorectal cancer screening [151] and transport [152]. In New Zealand, they have been applied to examine equity impacts of multiple tobacco control interventions [147, 153]; however, they have sparingly been applied in oral health to model equity impact of oral health interventions. This is a fertile research area, and oral epidemiologists again have an opportunity to utilise simulation modelling methods to generate evidence on long-term equity impact of dental public health interventions.

17.7 Way Forward and Conclusion

The burden of oral diseases and oral health inequalities is well established [22]. The recent publication of the Lancet Series on oral health recognises this challenge within the health community and provides a strong impetus to strengthen policy and research on oral health inequalities, an almost permanent associate of the burden of oral diseases [154]. Oral epidemiology will have to play a crucial role in generating quality evidence on policy solutions for reducing unfair and unjust socio-economic inequalities in oral health.

Harnessing the strengths from methodological advancements to enhance current knowledge on oral health inequalities will be a critical step. New techniques like prediction methods and machine learning, 'a set of methods that can automatically detect patterns in data, and then use the uncovered patterns to predict future data, or to perform other kinds of decision-making under uncertainty', are being applied within epidemiology to improve contemporary causal inference methods and exploit big data [31]. Enormous opportunities will be created to exploit such advancements for better understanding of oral health inequalities. Additionally, the use of geographic information systems, complex spatial statistics, systems science and qualitative research methods [155–157] can be further integrated into research on socio-economic inequalities in oral health.

In summary, it is vital to increase knowledge on policy solutions for addressing socio-economic inequalities in oral health. Theoretical and methodological aspects related to socio-economic inequalities in oral health must be considered carefully by oral epidemiologists. Methodological developments in epidemiology should

be capitalised for improving the current understanding of the relationship between socio-economic disadvantage and oral health, and more importantly, the solutions for addressing oral health inequalities.

References

1. Almeida A, Nunes BP, Duro SMS, Facchini LA. Socioeconomic determinants of access to health services among older adults: a systematic review. Rev Saude Publica. 2017;51:50.
2. Boing AF, Bastos JL, Peres KG, Antunes JL, Peres MA. Social determinants of health and dental caries in Brazil: a systematic review of the literature between 1999 and 2010. Rev Braz J Epidemiol. 2014;17(Suppl 2):102–15.
3. Costa SM, Martins CC, Pinto MQC, Vasconcelos M, Abreu M. Socioeconomic Factors and Caries in People between 19 and 60 Years of Age: An Update of a Systematic Review and Meta-Analysis of Observational Studies. Int J Environ Res Public Health. 2018;15(8):1775.
4. Harris R, Nicoll AD, Adair PM, Pine CM. Risk factors for dental caries in young children: a systematic review of the literature. Community Dent Health. 2004;21(1 Suppl):71–85.
5. Klein J, von dem Knesebeck O. Inequalities in health care utilization among migrants and non-migrants in Germany: a systematic review. Int J Equity Health. 2018;17(1):160.
6. Nobrega J, Dantas E, Ferreira-Filho JC, Limao N, Rodrigues-de-Melo AC, Protasio AP, et al. Contextual social inequities and occurrence of dental caries in adolescents: a systematic review. Oral Health Prev Dent. 2017;15(4):329–36.
7. Rai NK, Tiwari T. Parental factors influencing the development of early childhood caries in developing nations: a systematic review. Front Public Health. 2018;6:64.
8. Raison H, Harris RV. Interventions to reduce socio-economic inequalities in dental service utilisation – a systematic review. Community Dent Health. 2019;36(1):39–45.
9. Reda SF, Reda SM, Thomson WM, Schwendicke F. Inequality in utilization of dental services: a systematic review and meta-analysis. Am J Public Health. 2018;108(2):e1–7.
10. Reda SM, Krois J, Reda SF, Thomson WM, Schwendicke F. The impact of demographic, health-related and social factors on dental services utilization: systematic review and meta-analysis. J Dent. 2018;75:1–6.
11. Schwendicke F, Dorfer CE, Schlattmann P, Foster Page L, Thomson WM, Paris S. Socioeconomic inequality and caries: a systematic review and meta-analysis. J Dent Res. 2015;94(1):10–8.
12. Amarasena N, Ekanayaka AN, Herath L, Miyazaki H. Socio-demographic risk indicators for tooth mortality in rural Sri Lankans. Asia Pac J Public Health/Asia Pac Acad Consort Public Health. 2003;15(2):105–10.
13. Celeste RK, Nadanovsky P, Fritzell J. Trends in socioeconomic disparities in oral health in Brazil and Sweden. Community Dent Oral Epidemiol. 2011;39(3):204–12.
14. Do LG. Distribution of caries in children: variations between and within populations. J Dent Res. 2012;91(6):536–43.
15. Do LG, Spencer AJ, Slade GD, Ha DH, Roberts-Thomson KF, Liu P. Trend of income-related inequality of child oral health in Australia. J Dent Res. 2010;89(9):959–64.
16. Lopez R, Fernandez O, Baelum V. Social gradients in periodontal diseases among adolescents. Community Dent Oral Epidemiol. 2006;34(3):184–96.
17. Ravaghi V, Quinonez C, Allison PJ. Comparing inequalities in oral and general health: findings of the Canadian Health Measures Survey. Can J Public Health. 2013;104(7):e466–71.
18. Sabbah W, Tsakos G, Chandola T, Sheiham A, Watt RG. Social gradients in oral and general health. J Den Res. 2007;86(10):992–6.
19. Dye BA, Arevalo O, Vargas CM. Trends in paediatric dental caries by poverty status in the United States, 1988-1994 and 1999-2004. Int J Paediatr Dent. 2010;20(2):132–43.
20. Li KY, Okunseri CE, McGrath C, Wong MCM. Trends in self-reported oral health of US adults: National Health and Nutrition Examination Survey 1999-2014. Community Dent Oral Epidemiol. 2018;46(2):203–11.
21. Holst D. Oral health equality during 30 years in Norway. Community Dent Oral Epidemiol. 2008;36(4):326–34.
22. Watt RG, Heilmann A, Listl S, Peres MA. London charter on oral health inequalities. J Den Res. 2016;95(3):245–7.
23. Holst D. Causes and prevention of dental caries: a perspective on cases and incidence. Oral Health Prev Dent. 2005;3(1):9–14.
24. Holst D, Schuller AA, Aleksejuniene J, Eriksen HM. Caries in populations – a theoretical, causal approach. Eur J Oral Sci. 2001;109(3):143–8.
25. Watt RG. Social determinants of oral health inequalities: implications for action. Community Dent Oral Epidemiol. 2012;40(Suppl 2):44–8.
26. Watt RG. From victim blaming to upstream action: tackling the social determinants of oral health inequalities. Community Dent Oral Epidemiol. 2007;35(1):1–11.
27. Lorenc T, Petticrew M, Welch V, Tugwell P. What types of interventions generate inequalities? evidence from systematic reviews. J Epidemiol Community Health. 2013;67(2):190–3.
28. Singh A, Harford J, Peres MA. Investigating societal determinants of oral health-opportunities and challenges in multilevel studies. Community Dent Oral Epidemiol. 2018;46(4):317–27.
29. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annu Rev Public Health. 2000;21:121–45.
30. Nandi A, Harper S. How consequential is social epidemiology? A review of recent evidence. Curr Epidemiol Rep. 2014;2(1):61–70.
31. Blakely T, Lynch J, Simons K, Bentley R, Rose S, Reflection on modern methods: when worlds collide—prediction, machine learning and causal inference. Int J Epidemiol. dyz132, https://doi.org/10.1093/ije/dyz132.
32. Briggs ADM, Wolstenholme J, Blakely T, Scarborough P. Choosing an epidemiological model structure for the economic evaluation of non-communicable disease public health interventions. Popul Health Metrics. 2016;14(1):17.
33. Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. Soc Sci Med. 1997;44(6):757–71.
34. Mackenbach JP, Martikainen P, Menvielle G, de Gelder R. The arithmetic of reducing relative and absolute inequalities in health: a theoretical analysis illustrated with European mortality data. J Epidemiol Community Health. 2016;70(7):730–6.
35. WHO. Health Impact Assessment (HIA): Glossary of terms used Geneva: WHO. Available from: https://www.who.int/hia/about/glos/en/.
36. Whitehead M, Dahlgren G. Concepts and principles for tackling social inequities in health: levelling up part 1. WHO Regional Office for Europe: Copenhagen; 2006.
37. Sen A. Why health equity? Health Econ. 2002;11(8):659–66.
38. Singh A, Arora M, English DR, Mathur MR. Socioeconomic gradients in different types of tobacco use in India: evidence from global adult tobacco survey 2009-10. Biomed Res Int. 2015;2015:837804.
39. Sanders A, Slade G, Turrell G, John Spencer A, Marcenes W. The shape of the socioeconomic-oral health gradient: implications for theoretical explanations. Community Dent Oral Epidemiol. 2006;34(4):310–9.

40. Sanders AE, Spencer AJ. Social inequality in perceived oral health among adults in Australia. Aust N Z J Public Health. 2004;28(2):159–66.
41. Sanders AE, Spencer AJ, Slade GD. Evaluating the role of dental behaviour in oral health inequalities. Community Dent Oral Epidemiol. 2006;34(1):71–9.
42. Sabbah W, Watt RG, Sheiham A, Tsakos G. The role of cognitive ability in socio-economic inequalities in oral health. J Den Res. 2009;88(4):351–5.
43. Sabbah W, Tsakos G, Sheiham A, Watt RG. The role of health-related behaviors in the socioeconomic disparities in oral health. Soc Sci Med. 2009;68(2):298–303.
44. Singh A, Rouxel P, Watt RG, Tsakos G. Social inequalities in clustering of oral health related behaviors in a national sample of British adults. Prev Med. 2013;57(2):102–6.
45. Guarnizo-Herreno CC, Tsakos G, Sheiham A, Marmot MG, Kawachi I, Watt RG. Austin Powers bites back: a cross sectional comparison of US and English national oral health surveys. BMJ. 2015;351:h6543.
46. Guarnizo-Herreno CC, Watt RG, Pikhart H, Sheiham A, Tsakos G. Socioeconomic inequalities in oral health in different European welfare state regimes. J Epidemiol Community Health. 2013;67(9):728–35.
47. Peres MA, Luzzi L, Peres KG, Sabbah W, Antunes JL, Do LG. Income-related inequalities in inadequate dentition over time in Australia, Brazil and USA adults. Community Dent Oral Epidemiol. 2015;43(3):217–25.
48. Frohlich KL, Potvin L. Transcending the known in public health practice: the inequality paradox: the population approach and vulnerable populations. Am J Public Health. 2008;98(2):216–21.
49. Vanderbilt AA, Isringhausen KT, VanderWielen LM, Wright MS, Slashcheva LD, Madden MA. Health disparities among highly vulnerable populations in the United States: a call to action for medical and oral health care. Med Educ Online. 2013;18:1–3.
50. Sisson KL. Theoretical explanations for social inequalities in oral health. Community Dent Oral Epidemiol. 2007;35(2): 81–8.
51. Singh A, Harford J, Schuch HS, Watt RG, Peres MA. Theoretical basis and explanation for the relationship between area-level social inequalities and population oral health outcomes - A scoping review. SSM Popul Health. 2016;2:451–62.
52. Townsend P, Davidson N, Black DS. Inequalities in health : the Black report. Townsend P, Davidson N, Black DS, Great Britain. Working group on inequalities in health, editors. Harmondsworth: Penguin; 1982.
53. Bartley M. Health inequality : an introduction to theories, concepts, and methods. Cambridge, UK: Polity Press; 2004.
54. McCartney G, Collins C, Mackenzie M. What (or who) causes health inequalities: theories, evidence and implications? Health Policy. 2013;113(3):221–7.
55. Schuch HS, Peres KG, Singh A, Peres MA, Do LG. Socioeconomic position during life and periodontitis in adulthood: a systematic review. Community Dent Oral Epidemiol. 2017;45(3):201–8.
56. Schuch HS, Nascimento GG, Peres KG, et al. The Controlled Direct Effect of Early-Life Socioeconomic Position on Periodontitis in a Birth Cohort. Am J Epidemiol. 2019;188(6):1101–1108.
57. Poulton R, Caspi A, Milne BJ, Thomson WM, Taylor A, Sears MR, et al. Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. Lancet. 2002;360(9346):1640–5.
58. Peres MA, de Oliveira LMR, Sheiham A, Peres KG, Barros FC, Hernandez PG, et al. Social and biological early life influences on severity of dental caries in children aged 6 years. Community Dent Oral Epidemiol. 2005;33(1):53–63.
59. Peres MA, Peres KG, de Barros AJ, Victora CG. The relation between family socioeconomic trajectories from childhood to adolescence and dental caries and associated oral behaviours. J Epidemiol Community Health. 2007;61(2):141–5.
60. Sanders AE, Slade GD, Turrell G, Spencer AJ, Marcenes W. Does psychological stress mediate social deprivation in tooth loss? J Den Res. 2007;86(12):1166–70.
61. MacIntyre S. The Black report and beyond: what are the issues? Soc Sci Med. 1997;44:723–45.
62. Wilkinson RG. Socioeconomic determinants of health. Health inequalities: relative or absolute material standards? BMJ. 1997;314(7080):591–5.
63. Marmot M, Wilkinson R. Psychosocial and material pathways in the relation between income and health: a response to Lynch et al. BMJ. 2000;322:1233–6.
64. Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. Int J Epidemiol. 2002;31(6):1091–3.
65. Macinko JA, Shi L, Starfield B, Wulu JT Jr. Income inequality and health: a critical review of the literature. Med Care Res Rev. 2003;60(4):407–52.
66. Kawachi I, Kennedy BP, Lochner K, Prothrow-Stith D. Social capital, income inequality, and mortality. Am J Public Health. 1997;87(9):1491–8.
67. Lynch J. Income inequality and health: expanding the debate. Soc Sci Med. 2000;51(7):1001–5; discussion 9-10.
68. Lynch JW, Smith GD, Kaplan GA, House JS. Income inequality and mortality: importance to health of individual income, psychosocial environment, or material conditions. BMJ. 2000;320(7243):1200–4.
69. Lynch J, Smith GD, Harper S, Hillemeier M, Ross N, Kaplan GA, et al. Is income inequality a determinant of population health? Part 1. A Systematic Review. Milbank Q. 2004;82(1):5–99.
70. Muntaner C, Lynch J. Income inequality, social cohesion, and class relations: A critique of Wilkinson's neo-Durkheimian research program. Int J Health Serv. 1999;29(1):59–81.
71. Muntaner C, Rai N, Ng E, Chung H. Social class, politics, and the spirit level: why income inequality remains unexplained and unsolved. Int J Health Serv. 2012;42(3):369–81.
72. Sabbah W, Watt RG, Sheiham A, Tsakos G. Effects of allostatic load on the social gradient in ischaemic heart disease and periodontal disease: evidence from the Third National Health and Nutrition Examination Survey. J Epidemiol Community Health. 2008;62(5):415–20.
73. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285–93.
74. Peres MA, Peres KG, Thomson WM, Broadbent JM, Gigante DP, Horta BL. The influence of family income trajectories from birth to adulthood on adult oral health: findings from the 1982 Pelotas birth cohort. Am J Public Health. 2011;101(4):730–6.
75. Schuch HS, Peres KG, Demarco FF, Horta BL, Gigante DP, Peres MA, et al. Effect of life-course family income trajectories on periodontitis: birth cohort study. J Clin Periodontol. 2018;45(4):394–403.
76. Peres MA, Liu P, Demarco FF, Silva AER, Wehrmeister FC, Menezes AM, et al. Income trajectories affect treatment of dental caries from childhood to young adulthood: a birth cohort study. Braz Oral Res. 2018;32:e36.
77. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. Annu Rev Public Health. 1997;18:341–78.

78. Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. Epidemiol Rev. 1988;10:87–121.
79. Lombardi C, Bronfman M, Facchini LA, Victora CG, Barros FC, Beria JU, et al. Operationalization of the concept of social class in epidemiologic studies. Rev Saude Publica. 1988;22(4):253–65.
80. Berkman LF, Macintyre S. The measurement of social class in health studies: old measures and new formulations. IARC Sci Publ. 1997;138:51–64.
81. Barata RB, Ribeiro MC, Silva ZP, Antunes JL. Social class: concepts and operationalization models in health research. Rev Saude Publica. 2013;47(4):647–55.
82. Muntaner C, Borrell C, Vanroelen C, Chung H, Benach J, Kim IH, et al. Employment relations, social class and health: a review and analysis of conceptual and measurement alternatives. Soc Sci Med. 2010;71(12):2130–40.
83. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey SG. Indicators of socioeconomic position (part 2). J Epidemiol Community Health. 2006;60(2):95–101.
84. Castaneda H, Carrion IV, Kline N, Tyson DM. False hope: effects of social class and health policy on oral health inequalities for migrant farmworker families. Soc Sci Med. 2010;71(11):2028–37.
85. Delgado-Angulo EK, Bernabe E. Comparing lifecourse models of social class and adult oral health using the 1958 National Child Development Study. Community Dent Health. 2015;32(1):20–5.
86. Donaldson AN, Everitt B, Newton T, Steele J, Sherriff M, Bower E. The effects of social class and dental attendance on oral health. J Den Res. 2008;87(1):60–4.
87. Novrinda H, Han DH, Jung-Choi K, Ryu JI. Neo-Marxian social class inequalities in oral health among the south Korean population. Community Dent Oral Epidemiol. 2019;47(2):162–70.
88. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey SG. Indicators of socioeconomic position (part 1). J Epidemiol Community Health. 2006;60(1):7–12.
89. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122(12):2811–9.
90. Singh A, Peres MA, Watt RG. The relationship between income and oral health: A critical review. J Dent Res. 2019:0022034519849557.
91. Geyer S, Hemstrom O, Peter R, Vagero D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. J Epidemiol Community Health. 2006;60(9):804–10.
92. Green MJ, Popham F. Interpreting mutual adjustment for multiple indicators of socioeconomic position without committing mutual adjustment fallacies. BMC Public Health. 2019;19(1):10.
93. Hobdell M, Petersen PE, Clarkson J, Johnson N. Global goals for oral health 2020. Int Dent J. 2003;53(5):285–8.
94. Hobdell MH, Lalloo R, Myburgh NG. The human development index and per capita gross national product as predictors of dental caries prevalence in industrialized and industrializing countries. Ann N Y Acad Sci. 1999;896:329–31.
95. Hobdell MH, Oliveira ER, Bautista R, Myburgh NG, Lalloo R, Narendran S, et al. Oral diseases and socio-economic status (SES). Br Dent J. 2003;194(2):91–6; discussion 88
96. Lalloo R, Myburgh NG, Hobdell MH. Dental caries, socioeconomic development and national oral health policies. Int Dent J. 1999;49(4):196–202.
97. Aurelio Peres M, Glazer Peres K, Ferreira Antunes JL, Renno Junqueira S, Frazao P, Capel NP. The association between socioeconomic development at the town level and the distribution of dental caries in Brazilian children. Rev Panam Salud Publica. 2003;14(3):149–57.
98. Ekstrand KR, Christiansen ME, Qvist V, Ismail A. Factors associated with inter-municipality differences in dental caries experience among Danish adolescents. An ecological study. Community Dent Oral Epidemiol. 2010;38(1):29–42.
99. Tickle M, Craven R, Worthington HV. A comparison of the subjective oral health status of older adults from deprived and affluent communities. Community Dent Oral Epidemiol. 1997;25(3):217–22.
100. Sanders AE, Turrell G, Slade GD. Affluent neighborhoods reduce excess risk of tooth loss among the poor. J Den Res. 2008;87(10):969–73.
101. Locker D, Ford J. Using area-based measures of socioeconomic status in dental health services research. J Public Health Dent. 1996;56(2):69–75.
102. Locker D, Ford J. Evaluation of an area-based measure as an indicator of inequalities in oral health. Community Dent Oral Epidemiol. 1994;22(2):80–5.
103. Jagger DC, Sherriff A, Macpherson LM. Measuring socioeconomic inequalities in edentate Scottish adults--cross-sectional analyses using Scottish health surveys 1995-2008/09. Community Dent Oral Epidemiol. 2013;41(6):499–508.
104. Jones CM, Woods K, Taylor GO. Social deprivation and tooth decay in Scottish schoolchildren. Health Bull (Edinb). 1997;55(1):11–5.
105. Blakely TA, Woodward AJ. Ecological effects in multi-level studies. J Epidemiol Community Health. 2000;54(5):367–74.
106. Diez-Roux AV. Bringing context back into epidemiology: variables and fallacies in multilevel analysis. Am J Public Health. 1998;88(2):216–22.
107. Godoi H, Singh A, de Mello ALSF, Brennan DS, Peres MA. Area-level social development and indicators of public dental services in Southern Brazil. Community Dent Oral Epidemiol. 2019;47(3):274–80.
108. Bernabe E, Hobdell MH. Is income inequality related to childhood dental caries in rich countries? J Am Dent Assoc. 2010;141(2):143–9.
109. Merlo J, Wagner P, Ghith N, Leckie G. An original stepwise multilevel logistic regression analysis of discriminatory accuracy: the case of Neighbourhoods and health. PLoS One. 2016;11(4):e0153778.
110. Antunes JL, Peres MA, de Campos Mello TR, Waldman EA. Multilevel assessment of determinants of dental caries experience in Brazil. Community Dent Oral Epidemiol. 2006;34(2):146–52.
111. Freire MDM, Reis SCGB, Figueiredo N, Peres KG, Moreira RD, Antunes JLF. Individual and contextual determinants of dental caries in Brazilian 12-year-olds in 2010. Rev Saude Publica. 2013;47:40–9.
112. Guedes RS, Piovesan C, Antunes JL, Mendes FM, Ardenghi TM. Assessing individual and neighborhood social factors in child oral health-related quality of life: a multilevel analysis. Qual Life Res. 2014;23(9):2521–30.
113. Aida J, Ando Y, Oosaka M, Niimi K, Morita M. Contributions of social context to inequality in dental caries: a multilevel analysis of Japanese 3-year-old children. Community Dent Oral Epidemiol. 2008;36(2):149–56.
114. Aida J, Kondo K, Kondo N, Watt RG, Sheiham A, Tsakos G. Income inequality, social capital and self-rated health and dental status in older Japanese. Soc Sci Med. 2011;73(10):1561–8.
115. Bernabe E, Marcenes W. Income inequality and tooth loss in the United States. J Den Res. 2011;90(6):724–9.

116. Bower E, Gulliford M, Steele J, Newton T. Area deprivation and oral health in Scottish adults: a multilevel study. Community Dent Oral Epidemiol. 2007;35(2):118–29.
117. Choi YH, Lee SG. Does regional socioeconomic context affect the dental caries experience? A multilevel study of Korean adults. Eur J Oral Sci. 2011;119(4):294–300.
118. Koltermann AP, Giordani JM, Pattussi MP. The association between individual and contextual factors and functional dentition status among adults in Rio Grande do Sul state, Brazil: a multilevel study. Cad Saude Publica. 2011;27(1):173–82.
119. Peres MA, Peres KG, Frias AC, Antunes JL. Contextual and individual assessment of dental pain period prevalence in adolescents: a multilevel approach. BMC Oral Health. 2010;10:20.
120. Turrell G, Sanders AE, Slade GD, Spencer AJ, Marcenes W. The independent contribution of neighborhood disadvantage and individual-level socioeconomic position to self-reported oral health: a multilevel analysis. Community Dent Oral Epidemiol. 2007;35(3):195–206.
121. Regidor E. Measures of health inequalities: part 2. J Epidemiol Community Health. 2004;58(11):900.
122. Borrell LN, Talih M. A symmetrized Theil index measure of health disparities: an example using dental caries in U.S. children and adolescents. Stat Med. 2011;30(3):277–90.
123. Antunes JL, Narvai PC, Nugent ZJ. Measuring inequalities in the distribution of dental caries. Community Dent Oral Epidemiol. 2004;32(1):41–8.
124. Singh A, Peres MA, Watt RG. The relationship between income and Oral health: A critical review. J Den Res. 2019;98(8):853–60.
125. Shen J, Wildman J, Steele J. Measuring and decomposing oral health inequalities in an UK population. Community Dent Oral Epidemiol. 2013;41(6):481–9.
126. Ravaghi V, Quinonez C, Allison PJ. The magnitude of oral health inequalities in Canada: findings of the Canadian health measures survey. Community Dent Oral Epidemiol. 2013;41(6):490–8.
127. Harper S, King NB, Meersman SC, Reichman ME, Breen N, Lynch J. Implicit value judgments in the measurement of health inequalities. Milbank Q. 2010;88(1):4–29.
128. Celeste RK, Fritzell J. Do socioeconomic inequalities in pain, psychological distress and oral health increase or decrease over the life course? Evidence from Sweden over 43 years of follow-up. J Epidemiol Community Health. 2018;72(2):160–7.
129. Blakely T, Disney G, Atkinson J, Teng A, Mackenbach JP. A typology for charting socioeconomic mortality gradients: "Go Southwest". Epidemiology. 2017;28(4):594–603.
130. Kjellsson G, Gerdtham UG, Petrie D. Lies, damned lies, and health inequality measurements: understanding the value judgments. Epidemiology. 2015;26(5):673–80.
131. Kapilashrami A, Hankivsky O. Intersectionality and why it matters to global health. Lancet. 2018;391(10140):2589–91.
132. Merlo J. Multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA) within an intersectional framework. Soc Sci Med. 2018;203:74–80.
133. Evans CR, Williams DR, Onnela JP, Subramanian SV. A multilevel approach to modeling health inequalities at the intersection of multiple social identities. Soc Sci Med. 2018;203:64–73.
134. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012;41(2):514–20.
135. Nandi A, Glymour MM, Kawachi I, VanderWeele TJ. Using marginal structural models to estimate the direct effect of adverse childhood social conditions on onset of heart disease, diabetes, and stroke. Epidemiology. 2012;23(2):223–32.
136. Blakely T, Disney G, Valeri L, Atkinson J, Teng A, Wilson N, et al. Socioeconomic and tobacco mediation of ethnic inequalities in mortality over time: repeated census-mortality cohort studies, 1981 to 2011. Epidemiology. 2018;29(4):506–16.
137. Aitken Z, Simpson JA, Gurrin L, Bentley R, Kavanagh AM. Do material, psychosocial and behavioural factors mediate the relationship between disability acquisition and mental health? A sequential causal mediation analysis. Int J Epidemiol. 2018;47(3):829–40.
138. Chittleborough CR, Mittinty MN, Lawlor DA, Lynch JW. Effects of simulated interventions to improve school entry academic skills on socioeconomic inequalities in educational achievement. Child Dev. 2014;85(6):2247–62.
139. Fleischer NL, Diez Roux AV. Using directed acyclic graphs to guide analyses of neighbourhood health effects: an introduction. J Epidemiol Community Health. 2008;62(9):842–6.
140. Blinder AS. Wage discrimination: reduced form and structural estimates. J Hum Resour. 1973;8(4):436–55.
141. Oaxaca R. Male-female wage differentials in urban labor markets. Int Econ Rev. 1973;14(3):693–709.
142. Emamian MH, Zeraati H, Majdzadeh R, Shariati M, Hashemi H, Fotouhi A. The gap of visual impairment between economic groups in Shahroud, Iran: A Blinder-Oaxaca decomposition. Am J Epidemiol. 2011;173(12):1463–7.
143. Jiménez-Rubio D, Hernández-Quevedo C. Inequalities in the use of health services between immigrants and the native population in Spain: what is driving the differences? The Eur J Health Econ. 2011;12(1):17–28.
144. Peres MA, Ju X, Mittinty M, Spencer AJ, Do LG. Modifiable factors explain socioeconomic inequalities in children's dental caries. J Den Res. 2019;98(11):1211–8.
145. Farmer J, McLeod L, Siddiqi A, Ravaghi V, Quiñonez C. Towards an understanding of the structural determinants of oral health inequalities: A comparative analysis between Canada and the United States. SSM Popul Health. 2016;2:226–36.
146. Carter R, Moodie M, Markwick A, Magnus A, Vos T, Swinburn B, et al. Assessing cost-effectiveness in obesity (ACE-obesity): an overview of the ACE approach, economic methods and cost results. BMC Public Health. 2009;9:419.
147. Blakely T, Cobiac LJ, Cleghorn CL, Pearson AL, van der Deen FS, Kvizhinadze G, et al. Health, health inequality, and cost impacts of annual increases in tobacco tax: multistate life table modeling in New Zealand. PLoS Med. 2015;12(7):e1001856.
148. Singh A, Petrović-van der Deen FS, Carvalho N, Lopez AD, Blakely T. Impact of tax and tobacco-free generation on health-adjusted life years in the Solomon Islands: a multistate life table simulation. Tob Control. 2020;29(4):388–97.
149. Blakely T, Kvizhinadze G, Karvonen T, Pearson AL, Smith M, Wilson N. Cost-effectiveness and equity impacts of three HPV vaccination programmes for school-aged girls in New Zealand. Vaccine. 2014;32:2645–56.
150. Cobiac L, Tam K, Veerman L, Blakely T. Taxes and subsidies for improving diet and population health in Australia: A cost-effectiveness modelling study. PLoS Med. 2017;14(2):e1002232.
151. McLeod M, Kvizhinadze G, Boyd M, Barendregt J, Sarfati D, Wilson N, et al. Colorectal cancer screening: how health gains and cost-effectiveness vary by ethnic group, the impact on health inequalities, and the optimal age-range to screen. Cancer Epidemiol Biomark Prev. 2017;26(9):1391–400.
152. Mizdrak A, Blakely T, Cleghorn CL, Cobiac LJ. Potential of active transport to improve health, reduce healthcare costs, and reduce greenhouse gas emissions: A modelling study. PLoS One. 2019;14(7):e0219316.
153. Van der Deen FS, Wilson N, Cleghorn C, Kvizhinadze G, Cobiac L, Nghiem N, et al. Impact of five tobacco endgame strategies on future smoking prevalence, population health and health system costs: two modelling studies to inform the tobacco endgame. Tob Control. 2018;27(3):278–86.

154. Watt RG, Daly B, Allison P, Macpherson LMD, Venturelli R, Listl S, et al. Ending the neglect of global oral health: time for radical action. Lancet. 2019;394(10194):261–72.
155. Broomhead T, Baker SR. Systems science and oral health: implications for dental public health? Community Dent Health. 2019;36(1):55–62.
156. Broomhead T, Ballas D, Baker SR. Application of geographic information systems and simulation modelling to dental public health: where next? Community Dent Oral Epidemiol. 2019;47(1):1–11.
157. Gupta A, Keuskamp D. Use and misuse of mixed methods in population oral health research: A scoping review. Community Dent Health. 2018;35(2):109–18.

Further Reading

Arcaya MC, Arcaya AL, Subramanian SV. Inequalities in health: definitions, concepts, and theories. Glob Health Action. 2015;8:27106.
Bartley M. Health inequality : an introduction to theories, concepts, and methods. Cambridge, UK: Polity Press; 2004.
Costa-Font J, Hernandez-Quevedo C. Measuring inequalities in health: what do we know? What do we need to know? Health Policy. 2012;106(2):195–206.
Diez Roux AV. A glossary for multilevel analysis. J Epidemiol Community Health. 2002;56(8):588–94.
Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). J Epidemiol Community Health. 2006;60(1):7–12.
Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 2). J Epidemiol Community Health. 2006;60(2):95–101.
Harper S, King NB, Meersman SC, et al. Implicit value judgments in the measurement of health inequalities. Milbank Q. 2010;88(1):4–29.
Kawachi I, Subramanian SV, Almeida-Filho N. A glossary for health inequalities. J Epidemiol Community Health. 2002;56(9):647–52.
Krieger N. A glossary for social epidemiology. J Epidemiol Community Health. 2001;55:693–700.
Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. Soc Sci Med. 1997;44(6):757–71.
Sen A. Why health equity? Health Econ. 2002;11(8):659–66.
Singh A, Harford J, Schuch HS, et al. Theoretical basis and explanation for the relationship between area-level social inequalities and population oral health outcomes - A scoping review. SSM Popul Health. 2016;2:451–62.
Singh A, Harford J, Peres MA. Investigating societal determinants of oral health-opportunities and challenges in multilevel studies. Community Dent Oral Epidemiol. 2018;46(4):317–27.
Townsend P, Davidson N, Black DS. Inequalities in health : the Black report. Harmondsworth: Penguin; 1982.
Watt RG, Heilmann A, Listl S, et al. London charter on Oral health inequalities. J Dent Res. 2016;95(3):245–7.

Life Course Oral Health Epidemiology

Marco A. Peres, Karen Glazer Peres, Flavio Fernando Demarco, Marcos Britto Correa, and Anja Heilmann

Contents

18.1 Introduction – 296

18.2 The Development of Life Course Epidemiology – 296
18.2.1 Biological Programming – 296
18.2.2 Evidence of Risk Accumulation from Birth Cohort Studies – 296
18.2.3 A Life Course Perspective on Health Inequalities – 297

18.3 Life Course Theoretical Models: Critical Periods and Lifelong Risk Accumulation – 297
18.3.1 Critical Period/Sensitive Period Models – 297
18.3.2 Accumulation of Risk – 297
18.3.3 Chains of Risk (Pathway Models) – 298
18.3.4 Life Course Oral Health – 298
18.3.5 Oral Health Across the Life Cycle: Epidemiological Studies in Oral Health – 298
18.3.6 New Zealand Study: Dunedin – 298
18.3.7 The Pelotas, Brazil Birth Cohort Studies – 299
18.3.8 The Role of Socio-Economic Factors Across the Life Course on Oral Health – 301
18.3.9 The Relationship Between General and Oral Health – 302
18.3.10 Longitudinal Assessment of Sugar Consumption and Dental Caries – 303

18.4 Intergenerational Approach – 303
18.4.1 Predictive Models – 303

References – 304

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_18

Learning Objectives

- To introduce the main theories of life course epidemiology;
- To apply life course theories in oral health research;
- To show robust evidence of the link between socioeconomic position in the life course and oral health later;
- To investigate the relationship between oral and general health by using life course approaches;
- To demonstrate the unique contribution of cohort studies on the prediction of oral health outcomes

18.1 Introduction

Life course epidemiology has been defined as the study of the long-term effect on later health or disease risk of social or physical exposures during gestation, childhood, adolescence, young adulthood and later adult life [1]. This branch of epidemiology aims to understand the material, biological, behavioural and psychosocial processes operating across an individual's life course, or across generations, that are causally related to the development of disease risk.

A life course perspective is also key to understanding why social inequalities in health exist. In the twenty-first century, health inequalities are a major public health concern in most countries. A life course approach recognises that early life experiences and the accumulation of advantages and disadvantages throughout the life cycle combine to influence later disease risk. Health inequalities are therefore not just the result of current circumstances, but also of prior living conditions [2–5].

In relation to oral health, using a life course approach is arguably the most appropriate way of studying the most common dental diseases and disorders, namely dental caries, periodontal disease and their clinical endpoint of tooth loss. This is because these conditions are moderately or highly prevalent, they are chronic and cumulative, and their aetiologies are complex involving the interaction of social, biological and environmental factors [6].

This chapter presents the leading theories about the influence of the beginnings of life and their consequences for the state of future health. The recent applications of these theories in oral health are shown through examples particularly from two groups of birth cohort studies devoted to this theme. One of them is the Dunedin, New Zealand, Multidisciplinary Health and Development Study started in 1972, and another is a series of birth cohorts started in 1982, 1993, 2004 and 2015 in Pelotas, Brazil.

18.2 The Development of Life Course Epidemiology

Life course epidemiology is still a relatively young discipline, which emerged in the 1990s and took off since the start of the new Millennium. Its development was prompted by the findings from three areas of research: research on biological programming, emerging evidence of risk accumulation from birth cohort studies, and research into health inequalities and the social determinants of health [7].

18.2.1 Biological Programming

The biological programming hypothesis (also known as "fetal origins hypothesis" or "Barker hypothesis") was developed by a group of researchers at the University of Southampton, England, led by David Barker. It states that "fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programmes later coronary heart disease" [8]. Barker's theory is based on observations that low birth weight and small size during infancy, followed by accelerated weight gain during childhood, is predictive of later hypertension, heart disease and diabetes. These findings have been replicated in different populations [9, 10].

According to Barker's hypothesis, low birth weight serves as a marker of the intrauterine environment, indicating prenatal undernutrition. The foetus needs to adapt to the limited supply of nutrients to ensure immediate survival and to prepare itself for postnatal life, resulting in permanent effects on metabolism and physiology that may increase disease risk in later life. For example, foetal undernutrition may cause insulin resistance, which in turn may increase the risk of obesity and diabetes in adulthood if the subsequent childhood and adult environment is plentiful, or in other words, there is a mismatch between the prenatal and postnatal environment [11].

18.2.2 Evidence of Risk Accumulation from Birth Cohort Studies

The UK birth cohort studies are a rich and unique source of information on the material, behavioural and psychosocial factors influencing disease risk over time. Some of the early evidence about the influence of childhood experiences and risk accumulation across the life span on later adult health came from the first of the large UK birth cohort studies, the 1946 National Birth

Cohort, which follows the lives of all those born in one week of March 1946 in England, Wales and Scotland [12]. Data from this cohort has shed light on the influence of intrauterine growth, early childhood health and social circumstances on adult health (including such diverse outcomes as blood pressure and schizophrenia), as well as the adult socio-economic position. However, it appeared that these links were not inevitable, but were mediated or moderated by social and other risk factors operating throughout life [55]. One study showed how childhood respiratory illness was predicted by a combination of risk factors, namely a poor home environment, parental bronchitis and exposure to air pollution; and how childhood respiratory illness together with smoking in adulthood predicted adult lung disease [13].

18.2.3 A Life Course Perspective on Health Inequalities

The question how social conditions affect biological health outcomes – how 'life gets under the skin' – is fundamental to understanding why health inequalities exist. Social inequalities in health arise from the wider socio-political context which in turn influences patterns of social stratification, that is individuals' place in the social hierarchy according to their education, occupation and income (their socio-economic position or SEP). These are the structural determinants of health inequalities, which in turn affect intermediary determinants, including living and working conditions, exposure to psychosocial stress and health behaviours [14].

Explanations for health inequalities then include material, psychosocial and behavioural pathways, which are interrelated [4]. These pathways from social conditions to disease outcomes can only be fully understood when considering how they operate across the life cycle. For example, routine dental attendance is associated with better oral health over time [15]. Depending on the health care system, attendance (a behaviour) can be influenced by a person's income, that is, the material resources available to them. Indeed, dental attendance is socially patterned in many countries and such inequalities are already established during childhood [16].

Further, a person's socio-economic position is not fixed throughout life – it can change. Social mobility is commonly understood as the ability of individuals from disadvantaged backgrounds to move up in the world [17]. However, downward mobility is also possible. Intragenerational social mobility refers to changes in SEP within the same person during their lifetime, whereas intergenerational social mobility refers to the relationship between the SEP of parents and the status their children will attain as adults. Prospective cohort studies encompassing different life stages have shown that people who grow up in more favourable family environments in childhood have higher chances of acquiring a higher socio-economic position and achieving higher earnings as adults, and that stable high SEP throughout life as well as upward mobility are related to lower morbidity and mortality in adult life [17–20]. The degree to which childhood (parental) SEP predicts adult SEP varies between countries, with higher levels of upward social mobility seen in more egalitarian societies [21].

18.3 Life Course Theoretical Models: Critical Periods and Lifelong Risk Accumulation

The evidence on risk accumulation and the role of critical periods for health outcomes has led to the development of three main life course theoretical models.

18.3.1 Critical Period/Sensitive Period Models

Critical and sensitive period models focus on the importance of the timing of an exposure. A critical period is a limited time window in which an exposure can have adverse or protective effects [1]. Barker's biological programming hypothesis is an example of a critical period model. An oral health example of a critical period is the time of amelogenesis, when exposure to excess fluoride can result in dental fluorosis, or exposure to tetracycline can cause the discoloration of enamel. Sensitive periods are times of rapid developmental change, when an exposure has a stronger effect than it would have at other times, but where these effects are still modifiable or reversible [20]. Periods of human development that are considered sensitive include childhood and adolescence, labour market entry, the transition to parenthood, periods of insecurity at work and the time of departure from the labour market [22–27]. For example, cognitive stimulation during early childhood influences language development and later educational attainment [28–30].

18.3.2 Accumulation of Risk

Accumulation of risk models focus on the importance of exposure over time and the sequence of different exposures. Risk factors may be correlated (risk clustering) or independent [27]. Risk clustering occurs when an individual is exposed to several risk factors which

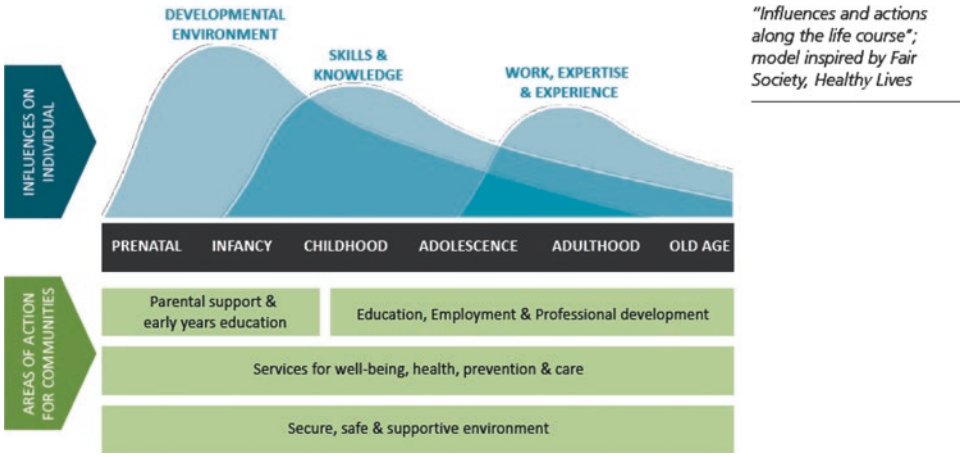


Fig. 18.1 Potential life course influences on oral health [35]

are related. For example, children from disadvantaged families might be exposed to diets high in sugar as well as irregular dental attendance, leading to an increased risk of dental caries. Both diet and dental attendance are related to family socio-economic position. An example of risk factors that are uncorrelated would be exposure to fluoridated drinking water and a diet low in sugar, which together reduce the risk of dental caries.

18.3.3 Chains of Risk (Pathway Models)

Early exposures may impact on disease outcome as well as increasing the likelihood of exposure to later risk factors. For example, poverty experienced in early childhood may lead to lower educational attainment, and both may increase the risk of poor adult oral health. If only the final link in the chain influences disease risk (stepping stone model), the chain can be broken, and disease can be prevented by addressing the earlier risk factors [1]. An example could be the intergenerational transmission of family violence.

18.3.4 Life Course Oral Health

Oral diseases and disorders such as dental caries, periodontal diseases and malocclusion are mainly of a chronic nature. For example, caries is a cumulative disease that progresses over time and may ultimately result in tooth loss. Longitudinal research has shown that the rates of increase in caries-affected tooth surfaces over the life course follow distinct trajectories, meaning that caries levels measured at one point in life predict caries levels at later ages, an important insight in relation to service planning [31, 32].

As the risk factors for systemic chronic diseases are common to those of the leading oral diseases [33, 34], it is reasonable to assume that the theoretical models explained so far can be used for oral health. This hypothesis guided the design of recent studies in the oral health area that are presented below. Figure 18.1 illustrates the life course influences on oral health.

18.3.5 Oral Health Across the Life Cycle: Epidemiological Studies in Oral Health

There are recent studies in the field of oral health that have adopted as a theoretical framework the accumulation of risks throughout the life cycle. The most appropriate design to investigate and test these hypotheses is the prospective cohort study. These studies are operationally tricky because they involve large samples, require technical capacity and high costs, which explains the limited availability of large cohort studies that include clinical dental data. However, there are a few still active birth cohort studies with oral health clinical assessments, particularly the Dunedin, New Zealand, study and the Pelotas, Brazil, studies. These cohort studies are multidisciplinary and multi-themed in nature, allowing the testing of theoretical hypotheses about oral health over the life course, from child development to adulthood.

18.3.6 New Zealand Study: Dunedin

A cohort of children born between April 1972 and March 1973 in Dunedin, New Zealand (the Dunedin Multidisciplinary Health and Development Study), has been investigated since the age of 3 years, comprising more than 1000 participants. The follow-up of this population included subsequent investigations at the ages of 5, 7, 9, 11, 13, 15, 18, 21, 26, 32 and 38 years of age with the collection of clinical oral health data at 5, 9, 15, 18, 26 and 38 years old. The participation rates

of this study are unusually high, and the participants attend the research unit within around 2 months of the date of their birthday for a full day of interviews and exams. The objectives of the study include investigating the relationship between socio-economic disadvantages experienced in the course of life and oral health outcomes; the relative importance of socio-economic conditions in childhood and adulthood; and the effects of changes in socio-economic circumstances throughout life (social mobility), on later life oral health [36].

All dental examinations are performed by two experienced researchers in the field of practice. At 26 years of age, the cohort underwent dental examinations that included measurements of dental plaque (using the Simplified Oral Hygiene index); gingival bleeding (measured tooth to tooth in two quadrants); periodontal attachment loss; and dental caries (using the DMFT index).

Childhood socio-economic position was captured using a combined measure of average parental income and education throughout childhood, when participants were aged 3–15 years, reflecting the conditions experienced by children during the period of growth and development. Socio-economic position in adulthood (26 years) was measured by the participants' own occupation. Studies on this cohort showed that better socio-economic conditions in childhood were linked to lower amounts of plaque, less gingival bleeding, a lower risk of periodontal disease and fewer decayed tooth surfaces at 26 years of age. As for the social mobility experienced since childhood, the results showed that downward mobility was associated with higher plaque accumulation. Compared to their more advantaged counterparts, adults who had lived in unfavourable socio-economic conditions during childhood had on average poorer general health – including an increased risk of obesity, increased systolic blood pressure, higher levels of cardiovascular disease and higher risk of alcohol dependence. The same phenomenon was observed concerning oral health outcomes such as higher plaque accumulation, gingival bleeding, periodontal disease and dental caries. As the analyses controlled for the effect of the social conditions experienced in the present (at 26 years), the results reinforce the hypothesis that the social origin plays a decisive role for adult health outcomes [36, 37].

At 32 years of age, new oral health data were collected, and analyses focused on patterns of dental attendance over the life course and their effects on oral health, as well as associations between the oral health of the previous generation (parents) and their children (cohort participants). Irregular dental attendance throughout life was associated with greater oral impacts on quality of life and worse self-assessment of oral health at 32 years of age [38]. Consistent associations between maternal oral health at the time when cohort participants were in their infancy and participants' own oral health in early adulthood were also identified. Adult children of mothers with worse oral health had poorer oral health and oral health-related quality of life, particularly on the sub-scale of psychological discomfort [39, 40]. Associations were found also between the periodontal health of parents and that of their adult children, suggesting that family history of oral health is a valid representation of the shared environmental and genetic factors that contribute to periodontal disease. This information can potentially assist in the prognosis of oral diseases and estimates of preventive treatment needs [41].

18.3.7 The Pelotas, Brazil Birth Cohort Studies

In the city of Pelotas, Southern Brazil, four birth cohort studies have been carried out since 1982; it is one of the few cities in the world with several population-based cohort studies. Barros and Victora [42] highlighted that the existence of longitudinal population-based studies conducted in the same site is unknown. The first cohort study of Pelotas births began in 1982, the second in 1993, the third in 2004 and the last one in 2015 totalling over 20,000 participants across all studies. Detailed trends in the health status of the citizens from Pelotas over more than 30 years have been published elsewhere [43].

Clinical oral health data were collected in each of these cohorts; for the 1982 cohort when the participants were 15, 24 and 31 years old; for the 1993 cohort at 6, 12 and 18 years of age; for the cohort of 2004 at the ages of 5 and 12 years, and the 2015 cohort started with oral examinations conducted among pregnant women. In some of the later waves, oral health topics were included in the questionnaires. It is anticipated that the collection of oral health data will continue as these cohorts are being followed up. Table 18.1 summarises the oral health-related modules of the questionnaires that were applied during all oral health assessments, while Table 18.2 displays oral health outcomes assessed in all cohorts.

Here, we would like to highlight the main findings of oral health studies conducted using data from the Pelotas birth cohort studies. We wish to cover some key areas such as the role of socio-economic change across the life course on oral health, the relationship between oral and general health, the prospective assessment of sugars consumption and dental caries, the intergenerational influence on oral health, and the predictive models to assess some oral health conditions.

Table 18.1 Oral health-related questionnaires modules in the different waves of oral health studies in the Pelotas birth cohorts

Modules	1982 cohort study			1993 cohort study			2004 cohort study		2015 cohort study			
	15 year	24 year	31 year	6 year	12 year	18 year	5 year	12 year	Pregnant	12 months	24 months	48 months
Oral health education	X			X				X	X	X	X	X
Dental care (use, reason, type, treatments received	X	X	X	X	X		X	X	X	X	X	X
Oral health-related habits and behaviours (breastfeeding, bottle feeding, non-nutritive sucking habits, mouth-breathe)	X			X						X	X	X
Oral hygiene (toothbrushing and flossing beginning and frequency)	X	X	X	X	X	X	X	X	X	X	X	X
Use of fluorides (water, toothpaste, supplements, mouth rinses, gels)	X		X		X	X	X	X		X	X	X
Self-rated oral health			X	X	X	X		X	X			X
Oral health-related quality of life			X		X		X	X				
Sugar consumption	X						X	X				X
Dental Fear							X					X
Bruxism								X				X
Family oral health (self-related measures)							X	X			X	
Dental Pain		X	X		X	X	X	X				X
Eruption of teeth										X	X	

Table 18.2 Oral health outcomes collected in the different waves of Pelotas birth cohorts

Dental data	1982 cohort study			1993 cohort study			2004 cohort study		2015 cohort study	
	15 year	24 year	31 year	6 year	12 year	18 year	5 year	12 year	Pregnant	4 year
Dental caries	X	X	X	X	X	X	X	X	X	X
Dental Plaque							X	X		X
Gingival bleeding		X	X		X			X	X	
Dental calculus		X	X					X	X	
Peridontal pocket		X	X						X	
CAL/gingival recession			X						X	
Mucosal lesions	X	X	X	X			X		X	
Dental fluorosis					X					
Dental trauma					X			X		X
Malocclusion	X			X	X		X	X		X
Quality of restorations		X	X					X		X
Tooth wear			X					X		X
Developmental Defects of enamel								X		X
Need for prosthesis		X	X							

18.3.8 The Role of Socio-Economic Factors Across the Life Course on Oral Health

The effect that socio-economic factors experienced during the life cycle have on oral health outcomes has been a main focus of studies using the Pelotas cohorts. Specifically, we investigated the effect of income trajectories on oral health later on. In the 1993 cohort, income data were assessed during five periods of life (at birth and at 4, 11, 15 and 18 years of age). Using a group-based trajectory analysis, Peres et al. [44] identified four income trajectory groups, classified as stable low-income, downward, upward and stable high-income, and tested their associations with dental caries increment from 6 to 18 years of age. No associations were found when the experience of dental caries, expressed by DMFT, was the outcome. However, family income trajectories over the life course affected increases in treated (FT) and untreated dental caries (DMT) from childhood to adulthood. Participants from stable low- and upward-income groups had higher levels of unsound teeth compared with those from the stable high-income group. On the other hand, the stable-low income group had fewer filled teeth than the high-level group. These findings highlight not only the effect of persistent relative poverty on oral health but also that the experience of at least one episode of poverty during the life cycle is sufficient to impact levels of disease. Long term follow-ups, from adolescence to adulthood, in the 1982 cohort have confirmed these findings and also corroborated the critical period hypotheses. Adults who were born into poverty had 30% more unsound teeth that those who were not [45].

Schuch et al. [46, 47] investigated whether income trajectories were associated with periodontitis at 31 years of age in the 1982 cohort. To model trajectories, income was measured at birth and ages 15, 19, 23 and 30 years. Three groups of income trajectories were identified and classified as ‘stable high’, ‘stable middle’ and ‘stable low and variable groups’ income. The results showed that the prevalence of moderate-to-severe periodontitis was more than 100% higher among participants from the stable low- and variable income group than among those from the stable high-income trajectory group [46]. In addition, participants who experienced the lowest socio-economic position early in life had a high risk of moderate-to-severe periodontitis in adulthood that was not mediated by adulthood socio-economic position and behaviour [47].

The direct effect of unfavourable socio-economic conditions on oral health has been confirmed by another study conducted among the Pelotas 1993 cohort. The most commonly used hypothesis to explain the effect of socio-economic status on periodontal health is via oral

health-related behaviours. Family income and education would be associated with the acquisition of healthy habits, including aspects related to nutrition and preventive care. To test this, Peres et al. [48] have investigated if oral health behaviours mediate the relationship between life course socio-economic circumstances and adolescents´ gingival bleeding in the 1993 cohort. The frequency of toothbrushing and dental visits in the last year were assessed at 6 and 12 years of age and considered as mediators. The results showed a direct effect of maternal education on adolescents´ gingival bleeding, which was not entirely mediated by oral health-related behaviours, suggesting that there is an alternative explanation for the effect of socio-economic position on gingival bleeding beyond oral health behaviours. This might suggest why strategies focusing on behaviour change tend to fail in reducing gingival bleeding. Public health strategies would be more effective if focused on more distal, upstream determinants.

Studies from the 1982 cohort have also focused on the role that socio-economic factors can play on the success of dental treatments, such as posterior direct restorations. Failures of direct restorations are caused mainly by caries and fracture of the tooth or restoration. The findings from the Pelotas cohort have consistently shown (at 24 and 31 years) that individuals from lower socio-economic groups presented more frequently with unsatisfactory restorations during the life cycle. The trajectory of dental caries was also strongly associated with restoration-related outcomes. Individuals with a high-risk income trajectory, that is, stable low-income during life had a higher risk for unsatisfactory restorations at age 31. Evidence from these studies support the hypothesis that individual socio-economic factors can be as crucial as technical aspects to increase the longevity of dental restorations [49, 50]. Individuals from the low-income background may have had lower quality dental care, and more deficient oral hygiene which in turn may have contributed to more restorations fails.

18

18.3.9 The Relationship Between General and Oral Health

An important strength of the Pelotas cohorts is their multidisciplinary nature, which allows the investigation of relationships between general and oral health outcomes in a population-based sample. The relationship between oral diseases, particularly periodontal disease and other chronic diseases has been investigated and become a hot topic in oral health research. To date, almost 100 associations between periodontal diseases and general health conditions have been reported [51]. However, a distinction between casual and causal association must be made (see a detailed explanation in the ▶ Chap. 16, Part II). Currently, there is still no evidence that treating oral disease has a meaningful effect on any systematic disease [52, 53]. A comprehensive discussion on the relationship between periodontal diseases and chronic diseases is covered in ▶ Chap. 25, Part II.

On the other hand, there is an increased body of evidence linking general health as a 'cause' and oral health as an 'effect'. The Pelotas cohort studies provide a unique opportunity to investigate such links due to their design, long follow up and the employment of new cutting-edge theoretical and analytical tools. In this chapter, we wish to cover two central relationships: the potential beneficial effect of breastfeeding on malocclusion and dental caries; and the impact of overweight and obesity on periodontal health.

The first study on the relationship between breastfeeding and malocclusion taking into account non-nutritive sucking habits was developed in the 1993 cohort when the children had all deciduous teeth [54]. Breastfeeding data were collected since birth and across several waves of the study, while malocclusion was assessed when children had their primary dentition completed. Traditional regression models including interaction tests between breastfeeding and use of pacifiers were performed. The findings revealed that breastfeeding for less than 9 months and regular use of pacifiers between age 12 months and 4 years were risk factors for a posterior cross bite. An interaction between the duration of breastfeeding and the pacifier use was identified for a posterior cross bite. Later on, using the larger sample of the 2004 Pelotas cohort study, the same hypothesis was tested, but this time the protective effect of exclusive and predominant breastfeeding was also tested [55]. The type of breastfeeding was recorded at birth and 3, 12 and 24 months of age. Open bite (OB), crossbite, overjet (OJ) and moderate/severe malocclusion (MSM) were assessed. Children who were exclusively breastfed from 3 to 5.9 months and up to 6 months of age had 41% and 72% lower prevalence of moderate and severe malocclusion, respectively, than those who were never breastfed. We have also investigated whether the duration of breastfeeding is a risk factor for dental caries regardless of sugar consumption in the same cohort. We used sophisticated theoretical and statistical models which allowed the estimation of the controlled direct effect of breastfeeding on severe early childhood caries (ECC). Prolonged breastfeeding (≥24 months) increased 2.4 times the risk of having ECC compared to those children who were breastfed up to 12 months. Breastfeeding between 13 and 23 months had no effects on ECC [56]. Preventive interventions for dental caries should be established as early as possible because breastfeeding is beneficial for children's health.

The study of Nascimento et al. [57] investigated the effect of obesity and overweight during the life cycle on

the risk of periodontitis at 31 years of age. Nutritional status of participants was assessed at 4, 15, 23 and 30 years of age and a set of time-varying covariates were also included in the analysis (smoking status, type 2 diabetes, hypertension and alcohol consumption). The parametric G-Formula was used to estimate the risk of periodontitis under hypothetical interventions in the studied populations. The findings suggest a dose–response relationship between overweight or obesity in the life cycle and periodontitis. Overweight and obesity increased the risk for all outcomes (any periodontitis; moderate-to-severe periodontitis; clinical attachment loss and; bleeding on probing). Also, when combined with other unhealthy habits, the risk for the outcomes was even greater [57]. In the same population, Nascimento et al. [58] investigated the association between Metabolic Syndrome (MetS) and periodontitis. MetS components included the level of HDL cholesterol, triglyceride levels and blood glucose, waist circumference and blood pressure. Structural Equation Modelling (SEM) was used to estimate the associations between variables. When both MetS and periodontitis were set as categorical observed variables, no association was found. However, MetS was positively associated with "advanced" periodontitis when latent variables were modelled but not with "initial" periodontitis. The use of latent variables to analyse both MetS and periodontitis allow to deal with multiple dimensions of these conditions, including prevalence, extension and severity, which is not possible using conventional categorical variables. Findings from the studies mentioned above confirm the relationship between general health characteristics experienced over the life course and periodontitis, suggesting the adoption of a common risk factor approach to prevent the occurrence of periodontal diseases.

18.3.10 Longitudinal Assessment of Sugar Consumption and Dental Caries

The effects of sugar consumption on dental caries from childhood to adolescence were studied using data from the 1993 cohort [59]. This is one of the very few longitudinal studies assessing sugar consumption and dental caries simultaneously. Group-based trajectory modelling was used to characterise trajectories of sugar consumption, collected at 4, 15 and 18 years of age. The increment of caries was assessed using three dental examinations performed at 6, 12 and 18 years of age. Three groups of sugar consumption trajectories were identified: high sugar consumption, upward and low sugar consumption. The results showed that dental caries increment was consistently and positively associated with high levels of sugar consumption during the life cycle. Both prevalence and experience of dental caries were higher for the highest sugar consumption group, although caries increased during the life course even in the low-sugar consumption group. The role of sugars in the development of several chronic conditions reinforces the need for policies focused on the promotion of healthy feeding practices.

18.4 Intergenerational Approach

The transmission of health across generations is seen as a function of gene–environment interactions that occur in a particular context [60], but it is barely found in the dental literature. One of the few notable exceptions is the work of Searer and colleagues from Dunedin, NZ [61]. In this study, the authors examined whether parental oral health history is a risk factor for dental caries and tooth loss later on, at the age of 32 years. Adults with poor oral health tended to have parents with poor oral health. The likelihood of following a high caries trajectory was twice as high for those in the high-family-risk group compared to the low-family-risk-group [61].

Inspired by the NZ colleagues, we have adopted a similar approach but using a shorter follow-up time. In the Pelotas 2004 cohort study, the mean dmfs of 5-year-old children was strongly associated with the mother's self-reported oral health. Children whose mothers reported excellent oral health had an average dmfs of 1.5 compared to 2.0 among those kids whose mothers reported average oral health, and 3.6 among children whose mothers reported poor and very poor oral health. Maternal oral-health behaviour had no direct effect on children's dental caries [62]. Instead, maternal oral health-related behaviours were related to maternal behaviour patterns such as the patterns of dental anxiety, toothbrushing and dental attendance.

18.4.1 Predictive Models

In the examples provided above, we have applied statistical models to data for testing a causal hypothesis about theoretical constructs. We have also provided examples of causal inference methods applicable to observational studies. We were in the field of explanation. Now we are going to move to the field of prediction. A predictive model is defined as the process of applying a statistical model for the purpose of predicting new or future observations [63]. Although explanatory modelling is commonly used for theory building and testing, predictive modelling is nearly absent in many scientific fields as a tool for developing theory. Now we will present some predictive models for dental caries and orthodontic treatment needs in adolescents, periodontitis in young adults, and need of dental prostheses among adults. For building these models, we have used dental and

other data from different waves of 1982, 1993 and 2004 Pelotas cohorts.

The first predictive model proposed was in the field of dental caries in the permanent dentition. A sample of the 1993 cohort study was dentally assessed at ages 6 and 12 years, and general and oral health-related data since birth were used to predict dental caries at 12 years old. Children who presented with a height-for-age deficit at 12 months, children who showed a DMFT of 1–3 and 4–19 at 6 years (RR = 2.01; CI: 95% = 1.33–3.03, and RR = 2.66; CI: 95% = 1.81–2.53, respectively) and children who aged 12 were in the highest tertile for the proportion of teeth with gingival bleeding presented a higher level of dental caries at age 12. However, the level of accuracy of the predictive model was modest with sensitivity and specificity values of around 60% [64].

The second predictive model was much more accurate than that described above for dental caries. This time we estimated orthodontic treatment needs among adolescents aged 12 years in the permanent dentition by using information collected over the life course. Malocclusion in the deciduous dentition was a powerful predictor for orthodontic treatment needs in adolescence. Children who had an open bite and canine malocclusion at the age of 6 years had an almost 12 times higher prevalence of mandatory orthodontic treatment need at age 12, compared to those who did not, after adjustment for anthropometric and dental-related variables. Children with malocclusion that is apparent at a young age should be monitored more frequently as their permanent teeth emerge, so that parents or caregivers can better prepare for possible orthodontic treatment [65].

The prediction of periodontitis has been challenging given there are few longitudinal studies with oral and general health data collected over a long period of follow up. In the 1982 Pelotas cohort study, we assessed the accuracy of predicting periodontal disease occurrence at age 31 years by using periodontal and other oral health-related data measured at age 24, along with several general health, socio-economic and demographic measures collected over the participants' life span [66]. Different periodontal disease case definitions were used with the highest sensitivity value (71.43%) for the Baelum and Lopez [67] case definition, having as the predictors the combination of the proportion of teeth with calculus, family income at birth, sex, diastolic blood pressure and DMFT at the age of 24 years.

The need for dental prostheses in young adulthood was predicted in the 1982 Pelotas cohort by using socio-economic and oral health-related data over the life course including the dental assessment at age 15 years [68]. The accuracy of predicting dental prosthesis at age 24 years using the decayed teeth component of the DMFT index at age 15 years was satisfactory (Sensitivity 71.7% and Specificity 66.1%) [68].

Final Remarks

This chapter described the emergence of life course epidemiology, their concepts and theories emphasising how they can be applied to oral health research. We have also tried to demonstrate the utility of life course epidemiology showing practical examples stem from the Pelotas birth cohort studies, a unique set of multidisciplinary and multi-themed investigations which included oral health sub-studies. We provided examples on the role of changes in socio-economic circumstances over the life course and their impact on oral different oral health outcomes, the relationship between general and oral health, the simultaneous trajectories of sugar consumption and dental caries from childhood to adolescence, and predictive models for periodontal disease, dental caries and orthodontic treatment. Relying on more than 20 years of research, we have tried to follow the methodological and theoretical developments of the discipline by using more sophisticated analytical tools in order to minimise biases. We have tried to demonstrate the advantages of having oral health studies nested in birth cohorts to answer some relevant research questions with also clear policy implications. By describing what we have done, we encourage our colleagues from different parts of the world to replicate our studies in order to build a robust body of evidence of some hot topics in oral health research.

References

1. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health. 2003;57(10):778–83.
2. Hertzman C. The biological embedding of early experience and its effects on health in adulthood. In: Adler N, Marmot M, Mcewen BS, Stewart J. Socioeconomic status and heath in industrial nations: social, psychological and biological pathways. Ann N Y Acad Sci. 1999;896:86–95.
3. Kawachi I, Berkman LF. A historical framework for social epidemiology. In: Kawachi I, Berkman LF, editors. Social epidemiology. New York: Oxford University Press; 2000. p. 3–12.
4. Bartley M. Health inequalities: an introduction to theories, concepts, methods. 2nd ed. Cambridge: Polity Press; 2017.
5. Richter M, Blane D. The life course: challenges and opportunities for public health research. Int J Public Health. 2013;58(1):1–2.
6. Nicolau B, Thomson WM, Steele JG, Allison PJ. Life-course epidemiology: concepts and theoretical models and its relevance to chronic oral conditions. Community Dent Oral Epidemiol. 2007;35(4):241–9.
7. Blane D, Netuveli G, Stone J. The development of life course epidemiology. Rev Epidemiol Sante Publique. 2007;55:31–8.
8. Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171–4.
9. Eriksson JG. The fetal origins hypothesis—10 years on. BMJ. 2005;330(7500):1096–7.
10. Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. Int J Epidemiol. 2011;40(3):647–61.

11. De Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol. 2006;46(1):4–14.
12. Kuh D, Richards M, Wadsworth M, Hardy R. Cohort profile: the 1946 National Birth Cohort (MRC National Survey of Health and Development). Int J Epidemiol. 2005;35(1):49–54.
13. Mann SL, Wadsworth MEJ, Colley JRT. Accumulation of factors influencing respiratory illness in members of a national birth cohort and their offspring. J Epidemiol Community Health. 1992;46:286–92.
14. WHO Commission on Social Determinants of Health. A conceptual framework for action on the social determinants of health. Discussion paper for the Commission on Social Determinants of Health – Last version. Geneva: World Health Organization; 2007.
15. Thomson WM, Williams SM, Broadbent JM, Poulton R, Locker D. Long-term dental visiting patterns and adult oral health. J Dent Res. 2010;89(3):307–11.
16. Listl S. Inequalities in dental attendance throughout the lifecourse. J Dent Res. 2012;91(7 Suppl):91S–7S.
17. Crawford C, Johnson P, Machin S, Vignoles A. Social mobility: a literature review. In: Economic policy reforms 2010: going for growth. Paris: OECD Publishing; 2011.
18. Kuh D, Wadsworth M. Childhood influences on adult male earnings in a longitudinal study. BJS. 1991;42:537–55.
19. Hemmingsson T, Lundberg I, Diderichsen F. The roles of social class of origin, achieved social class and intergenerational social mobility in explaining social-class inequalities in alcoholism among young men. Soc Sci Med. 1999;49:1051–9.
20. Corcoran ME, Chaudry A. The dynamics of childhood poverty. Futur Child. 1997;7(2):40–54.
21. OECD A broken social elevator? How to promote social mobility, OECD Publishing, Paris, 2018.
22. Bartley M, Blane D, Montgomery S. Socioeconomic determinants of health: health and the life course: why safety nets matter. BMJ. 1997;314:1194–201.
23. Smith GD, Hart C, Blane D, Gillis C, Hawthorne V. Lifetime socioeconomic position and mortality: prospective observational study. BMJ. 1997;314:547–58.
24. Power C, Hertzman C, Matthews S, Manor O. Social differences in health: life-cycle effects between ages 23 and 33 in the 1958 British Birth Cohort. Am J Public Health. 1997;87(9):1499–503.
25. Smith GD, Hart C, Blane D, Hole D. Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study. BMJ. 1998;316:1631–5.
26. Hart CL, Smith GD, Blane D. Inequalities in mortality by social class measured at 3 stages of the lifecourse. Am J Public Health. 1998;88(3):471–4.
27. Power C, Matthews S, Manor O. Inequalities in self-rated health: explanations from different stages of life. Lancet. 1998;351(9108):1009–14.
28. Davis-Kean PE. The influence of parent education and family income on child achievement: the indirect role of parental expectations and the home environment. J Fam Psychol. 2005;19(2):294–304.
29. Kelly Y, Sacker A, Del Bono E, Francesconi M, Marmot M. What role for the home learning environment and parenting in reducing the socioeconomic gradient in child development? Findings from the Millennium Cohort Study. Arch Dis Child. 2001;96(9):832–7.
30. Hart B, Risley TR. Meaningful differences in the everyday experience of young American children. Baltimore: Brookes; 1995.
31. Broadbent JM, Thomson WM, Poulton R. Trajectory patterns of dental caries experience in the permanent dentition to the fourth decade of life. J Dent Res. 2008;87(1):69–72.
32. Sheiham A, Sabbah W. Using universal patterns of caries for planning and evaluating dental care. Caries Res. 2010;44(2):141–50.
33. Hausen H. Caries predictors – state of the art. Community Dent Oral Epidemiol. 1997;2(1):87–96.
34. Sheiham A, Watt RG. The common risk approach: a rational approach for promoting oral health. Community Dent Oral Epidemiol. 2000;28:399–406.
35. Peres MA, Listl S, Heilmann A. Lifecourse oral health epidemiology. In: Watt RG, Listl S, Peres M, Heilmann A, editors. Social inequalities in oral health: from evidence to action. London: International Center for Oral health Inequalities Research and Policy, University College London; 2015. p. 16–7.
36. Poulton R, Caspi A, Milne BJ, Thomson WM, Taylor A, Sears MR, Moffitt TE. Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. Lancet. 2002;360(9346):1640–5.
37. Thomson WM, Poulton R, Milne BJ, Caspi A, Broughton JR, Ayers KM. Socioeconomic inequalities in oral health in childhood and adulthood in a birth cohort. Community Dent Oral Epidemiol. 2004;32(5):345–53.
38. Crocombe LA, Broadbent JM, Thomson WM, Brennan DS, Poulton R. Impact of dental visiting trajectory patterns on clinical oral health and oral health-related quality of life. J Public Health Dent. 2012;72(1):36–44.
39. Shearer DM, Thomson WM, Caspi A, Moffitt TE, Broadbent JM, Poulton R. Family history and oral health: findings from the Dunedin Study. Community Dent Oral Epidemiol. 2012;40(2):105–15.
40. Shearer DM, Thomson WM, Broadbent JM, Poulton R. Does maternal oral health predict child oral health-related quality of life in adulthood? Health Qual Life Outcomes. 2011;7(9):50.
41. Shearer DM, Thomson WM, Caspi A, Moffitt E, Broadbent JM, Poulton R. Inter-generational continuity in periodontal health: findings from the Dunedin family history study. J Clin Periodontol. 2011;38(4):301–9.
42. Barros FC, Victora CG. Maternal and Children Health in Pelotas, Rio Grande do Sul, Brazil, 1982–1993: A Decade of Transition. [Editorial]. Cad Saúde Pública. 1996;12(Suppl1):4–5.
43. Barros FC, Victora CG. Commentary: a tale of many cities in one: the Pelotas (Brazil) birth cohorts, 1982–2015. Int J Epidemiol. 2019;48(Suppl_1):i89–93.
44. Peres MA, Liu P, Demarco FF, Silva AER, Wehrmeister FC, Menezes AM, Peres KG. Income trajectories affect treatment of dental caries from childhood to young adulthood: a birth cohort study. Braz Oral Res. 2018;32:e36.
45. Peres MA, Peres KG, Thomson WM, Broadbent JM, Gigante DP, Horta BL. The influence of family income trajectories from birth to adulthood on adult oral health: findings from the 1982 Pelotas birth cohort. Am J Public Health. 2011;101(4):730–6.
46. Schuch HS, Peres KG, Demarco FF, Horta BL, Gigante DP, Peres MA, et al. Effect of life course family income trajectories on periodontitis: birth cohort study. J Clin Periodontol. 2018;45:394–403.
47. Schuch HS, Nascimento GG, Peres KG, Mittinty MN, Demarco FF, Correa MB, et al. The controlled direct effect of early life socioeconomic position on periodontitis in a birth cohort. Am J Epidemiol. 2019;188:1101–8.
48. Peres MA, Nascimento GG, Peres KG, Demarco FF, Menezes AB. Oral health-related behaviours do not mediate the effect of maternal education on adolescents' gingival bleeding: a birth cohort study. Community Dent Oral Epidemiol. 2018;46(4):317–27.
49. Correa MB, Peres MA, Peres KG, Horta BL, Barros AJ, Demarco FF. Do socioeconomic determinants affect the quality of posterior dental restorations? A multilevel approach. J Dent. 2013;41(11):960–7.

50. Collares K, Opdam NJ, Peres KG, Peres MA, Horta BL, Demarco FF, Correa MB. Higher experience of caries and lower income trajectory influence the quality of restorations: a multilevel analysis in a birth cohort. J Dent. 2018;68:79–84.
51. Bartold PM. Opportunistic dentistry is harming our credibility. Aust Dent J. 2018;63:269.
52. Pihlstrom BL, Hodges JS, Michalowicz B, Wohlfahrt JC, Garcia RI. Promoting oral health care because of its possible effect on systemic disease is premature and may be misleading. J Am Dent Assoc. 2018;149:401–3.
53. Leite F, Peres MA, Nascimento GG. Is the misinterpretation of association and causation a never-ending story? Aust Dent J. 2019;64:201–202.
54. Peres KG, Barros AJ, Peres MA, Victora CG. Effects of breastfeeding and sucking habits on malocclusion in a birth cohort study. Rev Saude Publica. 2007;41(3):343–50.
55. Peres KG, Cascaes AM, Peres MA, Demarco FF, Santos IS, Matijasevich A, et al. Exclusive breastfeeding and risk of dental malocclusion. Pediatrics. 2015;136(1):e60–7.
56. Peres KG, Nascimento GG, Peres MA, Mittinty MN, Demarco FF, Santos IS, Matijasevich A, et al. Impact of prolonged breastfeeding on dental caries: a population-based birth cohort study. Pediatrics. 2017;140(1):e20162943.
57. Nascimento GG, Peres MA, Mittinty MN, Peres KG, Do LG, Horta BL, et al. Diet-induced overweight and obesity and periodontitis risk: an application of the parametric G-formula in the 1982 Pelotas Birth Cohort. Am J Epidemiol. 2017;185:442–51.
58. Nascimento GG, Leite FRM, Peres KG, Demarco FF, Corrêa MB, Peres MA. Metabolic syndrome and periodontitis: a structural equation modeling approach. J Periodontol. 2019;90(6):655–662.
59. Peres MA, Sheiham A, Liu P, Demarco FF, Silva AE, Assunção MC, Menezes AM, Barros FC, Peres KG. Sugar consumption and changes in dental caries from childhood to adolescence. J Dent Res. 2016;95(4):388–94.
60. Cheng TL, Johnson SB, Goodman E. Breaking the intergenerational cycle of disadvantage: the three-generation approach. Pediatrics. 2016;137(6):e20152467.
61. Shearer DM, Thomson WM, Caspi A, Moffitt TE, Briadbent JM, Poulton R. Family history and oral health: findings from the Dunedin Study. Community Dent Oral Epidemiol. 2013;40(2):105–15.
62. Goettems ML, Nascimento GG, Peres MA, Santos IS, Matijasevich A, Barros AJD, et al. Influence of maternal characteristics and caregiving behaviours on children's caries experience: an intergenerational approach. Community Dent Oral Epidemiol. 2018;46(5):435–41.
63. Shmueli G. To explain or to predict. Stat Sci. 2010;25(3):289–310.
64. Peres MA, Barros AJ, Peres KG, Araújo CL, Menezes AM. Life course dental caries determinants and predictors in children aged 12 years: a population-based birth cohort. Community Dent Oral Epidemiol. 2009;37(2):123–33.
65. Peres KG, Peres MA, Thomson WM, Broadbent J, Hallal PC, Menezes AMB. Deciduous-dentition malocclusion predicts orthodontic treatment needs later: findings from a population-based birth cohort study. Am J Orthod Dentofacial Orthop. 2015;147:492–8.
66. Leite FR, Peres KG, Do LG, Demarco FF, Peres MA. Prediction of periodontitis occurrence: influence of the classification, sociodemographic and general health information. J Periodontol. 2017;88:731–43.
67. Baelum V, Lopez R. Defining a periodontitis case: analysis of a never-treated adult population. J Clin Periodontol. 2012;39:10–9.
68. Correa MB, Peres MA, Peres KG, Horta BL, Gigante DP, Demarco FF. Life-course determinants of need for dental prostheses at age 24. J Dent Res. 2010;89(7):733–8.

Further Reading

Journal of Development Origins of Health and Disease (JDOHaD) is a multidisciplinary journal which publishes work in developmental programming, foetal and neonatal biology and physiology, early life nutrition, particularly during the first 1,000 days of life, human ecology and evolution and gene-environment interactions. The journal also publishes articles that address the social determinants or education of health and disease risk as they relate to the early life period, as well as the economic and health care costs of a poor start to life.

Moffitt TE, Belsky DW, Danese A, Poulton R, Caspi A. The longitudinal study of aging in human young adults: knowledge gaps and research agenda. J Gerontol A Biol Sci Med Sci. 2017;72(2):210–5.

Peres MA, Barros AJ, Peres KG, Araújo CL, Menezes AM, Hallal PC, Victora CG. Oral health follow-up studies in the 1993 Pelotas (Brazil) birth cohort study: methodology and principal results. Cad Saude Publica. 2010;26(10):1990–9.

Peres KG, Peres MA, Demarco FF, Tarquínio SB, Horta BL, Gigante DP. Oral health studies in the 1982 Pelotas (Brazil) birth cohort: methodology and principal results at 15 and 24 years of age. Cad Saude Publica. 2011;27(8):1569–80.

Silva PA, Stanton W, editors. From childhood to adult: the Dunedin multidiscipinary health and development study. Oxford: Oxford University Press; 1997.

The Dunedin Study webpage. https://dunedinstudy.otago.ac.nz/.

The Pelotas birth cohort studies webpage. http://www.epidemio-ufpel.org.br/site/content/studies/.

Sugar Consumption and Oral Health

Anja Heilmann, Carolina Machuca Vargas, and Richard G. Watt

Contents

19.1 Introduction – 308

19.2 WHO Classification of Sugars and Guideline on Sugars Intake – 308

19.2.1 WHO Classification of Sugars – 308

19.2.2 Current WHO Guideline on Sugars Intake – 308

19.3 The Role of Free Sugars for Oral and General Health – 309

19.3.1 Free Sugars and Oral Health – 309

19.3.2 Free Sugars and General Health – 310

19.4 Patterns and Trends in Free Sugars Consumption – 311

19.5 Social and Commercial Determinants of Sugar Consumption – 313

19.6 Policy Action to Reduce Sugar Consumption – 314

19.7 Conclusion – 315

References – 315

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_19

Learning Objectives

- Describe the WHO classification of sugars and WHO guidelines on free sugars intake.
- Describe global trends in sugar consumption.
- Outline and discuss the evidence on causal links between consumption of free sugars, oral and general health.
- Explain what is meant by the 'social and commercial determinants of health'.
- Identify upstream, midstream and downstream policy strategies to reduce sugar intake at population and individual levels.

19.1 Introduction

Dental caries is the most common of all chronic conditions worldwide. In 2015, the global prevalence of untreated caries in permanent teeth was 34% for all ages combined [1]. This presents an enormous public health challenge that requires a response beyond the provision of dental treatment, which is unaffordable in many low- and middle-income countries [2, 3]. We cannot treat the problem away; instead, we need to tackle the causes, and the main causal factor in the development of dental caries are dietary sugars [4, 5].

Sugar is increasingly recognised as a global public health issue and commercial determinant of health. Excess sugar consumption not only causes dental caries but is also implicated in a range of other major non-communicable diseases, including obesity, diabetes and cardiovascular disease [6]. Sugar is cheap and easily available, and its consumption in high- and middle-income countries far exceeds public health recommendations. But dietary habits including sugar consumption are not simply 'lifestyle choices' that people make in a vacuum. They are influenced by a wide range of factors in the immediate and wider social and political environment, most of which are outside the control of individuals. To prevent oral diseases, these social determinants of health need to be addressed [3, 7].

The power imbalance between the public health community and the vested commercial interests of the sugar industry presents an additional major challenge. Sugar is big business. Profit margins are high, and the industry is aggressively marketing their unhealthy products, which includes the direct targeting of children. With markets close to saturation in high-income countries, the industry's attention has shifted to targeting emerging economies [8]. For example, by 2020 Coca-Cola intends to spend $12 billion on marketing across Africa [9]. Compare this to the total annual WHO budget for 2017, which was $4.4 billion [3]. The financial power of Big Sugar means that, in many countries, these companies have disproportionate influence over policy decisions affecting population health. But policymakers can use their power to regulate – tobacco control policies are a prime example of successful regulation. As this chapter will show, oral health professionals have an important role to play in this, as strong advocates for action on the social determinants of health and the regulation of the food and drinks industry.

19.2 WHO Classification of Sugars and Guideline on Sugars Intake

19.2.1 WHO Classification of Sugars

Several sugar classifications exist, and their varying nature can sometimes be confusing. Here, we are using the term 'free sugars' when referring to the dietary sugars that are most relevant to health, based on the classification recommended by the WHO in their 2015 guideline on sugar intake (Fig. 19.1) [5]. According to this, total sugars are all mono- and disaccharides from any dietary source [10]. Total sugars include intrinsic sugars, which are naturally present within the cell structure of intact fruits and vegetables; milk sugars, which are naturally present in milk and milk products; and free sugars, which are defined as 'all monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates' [5].

Intrinsic sugars and milk sugars do not have adverse effects on oral or general health [5]. Therefore, current dietary recommendations by WHO and other health organisations refer to free sugars. Free sugars are therefore the focus of this chapter.

19.2.2 Current WHO Guideline on Sugars Intake

In 2015, the WHO published updated guidance on sugars intake for adults and children [5]. The overall purpose of the WHO guideline was to provide evidence-based recommendations that can be used by policymakers aiming to reduce the risk of non-communicable diseases, focusing in particular on the prevention of unhealthy weight gain and dental caries.

The WHO guideline makes three recommendations for both children and adults:

1. 'WHO recommends a reduced intake of free sugars throughout the lifecourse (strong recommendation)'.
2. 'In both adults and children, WHO recommends reducing the intake of free sugars to less than 10% of total energy intake (strong recommendation)'.
3. 'WHO suggests a further reduction of the intake of free sugars to below 5% of total energy intake (conditional recommendation)'.

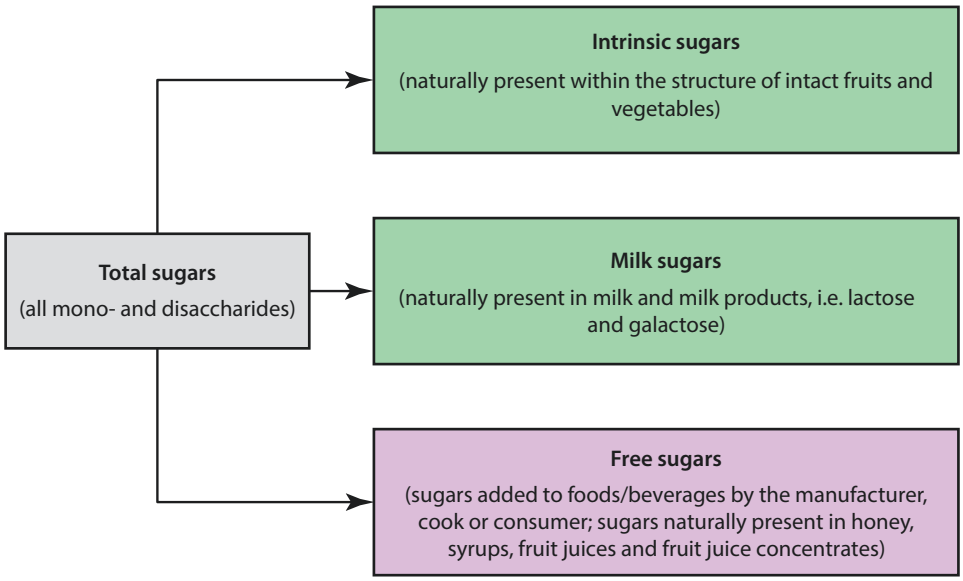


Fig. 19.1 Classification of sugars (WHO 2015)

Strong recommendations are made where 'the desirable effects of adherence to the recommendation outweigh the undesirable consequences' and the recommendation can be adopted in most situations. Conditional recommendations are made when 'there is less certainty about the balance between the benefits and harms or disadvantages of implementing a recommendation' and policymakers should consult with relevant stakeholders before such recommendations are adopted [5].

It should be emphasised that these recommendations refer to maximum amounts. For the average adult, 10% of total energy intake translates to about 50 grams per day, or about 10 teaspoons; and 5% of total energy intake equal about 25 grams per day (5 teaspoons) [11]. To illustrate, 200 ml orange juice contain about 20 grams of free sugar, and a 330 ml cola drink contains about 35 grams.

The above recommendations were informed by two systematic reviews that were commissioned by the WHO for this purpose [12, 13]. Their findings are summarised in the following sections.

19.3 The Role of Free Sugars for Oral and General Health

19.3.1 Free Sugars and Oral Health

19.3.1.1 Dental Caries

The portrayal of dental caries as a multifactorial disease is still common. This is, however, unhelpful and potentially misleading, because dental caries is caused by one specific factor: dietary (free) sugars [14]. While factors such as salivary flow and fluoride exposure play a role in the caries process, these are effect modifiers; in other words, they influence the strength of the association between sugar consumption and caries development. Caries is not caused by a lack of fluoride – fluoride merely helps to delay the process [15]. The decisive causal factor that needs to be present for caries to develop is sugar [14].

The evidence for the pivotal role of free sugars in the development of dental caries is consistent and based on more than 60 years of research that includes a range of different study designs, such as epidemiological studies, human intervention studies and animal studies. The international evidence was most recently appraised by Moynihan and Kelly in 2015, in a systematic review commissioned by the WHO that subsequently informed the current WHO recommendations on sugar intake [5, 13].

The review by Moynihan and Kelly [13] aimed to evaluate the evidence on the association between the amount of sugars intake and dental caries and to assess the effect of restricting sugar intake to less than 10% and less than 5% of total energy intake. Fifty-five studies met the inclusion criteria. Considered were papers published between 1950 and 2011 that reported studies with intervention, cohort, population, and cross-sectional designs. The overall quality of the available evidence was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [16]. The majority of the included studies were cross-sectional and conducted in children. Eight were cohort studies providing evidence on the effect of increasing or reducing sugar consumption. Overall, there was consistent evidence, judged to be of moderate quality, in support of an association between the amount of sugars consumed and the development of dental caries, and evidence of a dose–response relationship. Further, there was evidence

of moderate quality that reducing sugars intake to less than 10% of total energy intake is associated with lower levels of caries. It should be emphasised that these studies took fluoride exposure into account and that the relationship between sugars and dental caries remained despite the protection offered by fluoride. Restricting sugar intake to less than 5% of total energy was associated with further benefits in terms of caries reduction. While the evidence in relation to the 5% limit was sparse and judged to be of very low quality, these additional benefits are potentially important given the chronic and progressive nature of dental caries. In the United Kingdom, the available evidence has led the Scientific Advisory Committee on Nutrition (SACN) to revise its previous recommendation on sugar intake downward, from 10% to no more than 5% of total dietary energy for all age groups from 2 years upwards [17].

Most of the above described evidence comes from studies conducted on children, often aged 12 years, when permanent teeth are newly erupted. It is important to bear in mind that dental caries is a progressive disease, and that in high-income countries in particular, most dental caries is now occurring in adults [14]. This means that from a life course perspective, even small reductions in dental caries at younger ages have important benefits over time [13].

Dried Fruit

The WHO definition of free sugars does not include sugars contained in dried fruit. But are the sugars contained in dried fruit cariogenic? Currently, epidemiological evidence to answer this question is lacking. Consideration should be given to the fact that dried fruits (not containing added sugars) are a good source of dietary fibre and some micronutrients while also containing a high concentration of free sugars. Therefore, the consumption of dried fruit should be limited to mealtimes and not exceed more than one portion a day [11].

Intrinsic Sugars Present in Fresh Fruits and Vegetables

Fruits and vegetables are a very important part of a healthy diet because of the fibre and micronutrients they contain, and their consumption should be strongly encouraged. Diets low in fruits and vegetables have been linked to an increased risk of weight gain, as well as a higher risk of developing different types of cancers, including oral cancers [18, 19]. Intrinsic sugars present in fresh fruits and vegetables are not cariogenic, and dental professionals should encourage their patients to eat them [18, 20].

Milk Sugars

Milk (cow's milk and breast milk) contains milk sugar (lactose) and calcium. The sweetness and cariogenicity of lactose are very low [20]. As long as no sugars or sugary flavourings are added to it, the consumption of cow's milk is considered safe for dental health. Indeed, water and milk are recommended as healthy drinks for children [11]. A systematic review on breastfeeding and dental caries concluded that breastfeeding within the first year is associated with a decreased risk of dental caries [21]. For children older than 12 months, the currently available evidence is inconclusive, as other factors come into play such as complementary feeding of sugary foods and drinks, and tooth brushing habits [22]. Given the strong evidence for the beneficial effects of breastfeeding on child health and development [23], dental health professionals should support WHO guidance on breastfeeding, which states that 'infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health, and thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to two years of age or beyond' [24].

Frequency or Amount of Free Sugars?

Both the total amount of free sugars and the frequency of their consumption play a role in the caries process; however, evidence on the relative importance of these two factors is limited [17]. The above described systematic review by Moynihan and Kelly [13] has focused on amount of intake in line with taking a Common Risk Factor Approach, as the WHO guideline relates to both oral and general health and amount of intake is of particular importance for weight gain and other general health outcomes. Given that both amount and frequency of sugar intake are highly correlated in human diets [25], an appropriate caries prevention strategy should emphasise the importance of reducing the amount of intake, while highlighting that reducing the frequency of intake can help to achieve this aim [11].

19.3.1.2 Periodontal Disease

The dietary risk factors best known for their association with periodontal disease are deficiencies of vitamins C and D, and low calcium levels [26, 27]. However, emerging evidence suggests that a high consumption of added sugars is also associated with an increased risk of periodontal disease [28, 29]. The biological mechanism is likely to involve dietary refined carbohydrates generating oxidative stress, which plays an important role in the pathogenesis of chronic inflammatory diseases including periodontitis [26, 29].

19.3.2 Free Sugars and General Health

19.3.2.1 Unhealthy Weight Gain

There is strong evidence that the consumption of free sugars, in particular from sugar-sweetened beverages (SSB), is a determinant of excess body weight. A systematic review and meta-analyses of randomised controlled

trials and prospective cohort studies, commissioned to inform the WHO guideline on sugars intake and published in 2013 by Te Morenga and colleagues, found that SSB are a major driver of unhealthy weight gain [12]. The WHO-commissioned review included 30 trials and 38 cohort studies on adults and children. The trial evidence consistently showed that among adults with ad libitum diets, increased or decreased intake of free sugars was associated with a corresponding increase or decrease in body weight. Findings from cohort studies were similar and based mainly on studies assessing the consumption of SSB. For children, the trial evidence was inconclusive, likely due to poor compliance with dietary interventions. The findings suggest that the main mechanism through which sugar consumption promotes weight gain is via an increase in overall energy intake, leading to an imbalance between energy intake and output. Sugar-sweetened beverages due to their liquid form are thought to be less satiating than solid foods, and therefore to encourage excess overall energy consumption [12].

The findings of the WHO-commissioned review are supported by a number of other systematic reviews. The evidence is particularly strong for the association between high levels of SSB consumption and weight gain [30–35]. It needs to be highlighted here that systematic reviews not supporting a link between SSB and weight gain are mainly funded by the food and drink industry: a 2014 'systematic review of systematic reviews' found that industry-funded reviews were five times more likely to present a conclusion of no positive association than those that had not declared such conflicts of interest [36].

19.3.2.2 Diabetes

Systematic reviews have consistently shown links between greater consumption of sugar-sweetened beverages and an increased risk of type 2 diabetes mellitus [6, 37–40]. There is also evidence that higher availability of free sugars is associated with higher prevalence of type 2 diabetes at country level: an econometric analysis including repeated cross-sectional data from 175 countries found that every 150 kcal/person/day increase in sugar availability was associated with increased diabetes prevalence by 1.1%, after wide-ranging adjustments [41].

The relationship between consumption of free sugars and type 2 diabetes has been reviewed by Lean and Te Morenga in 2016, with a particular focus on whether any links are indeed causal [42]. For a causal relationship to exist, studies would need to demonstrate that consumption of free sugars has an independent effect on diabetes onset or progression or that sugar consumption contributes to disease onset by causing unhealthy weight gain. There is wide-ranging consensus that weight gain is causally related to diabetes onset and that overweight and obesity are among the most important risk factors for type 2 diabetes [43–46]. Human intervention studies have shown that weight loss interventions are effective in preventing type 2 diabetes and that significant weight loss can reverse existing diabetes, i.e. lead to remission [12, 47]. The pathway via overweight and obesity is supported by studies investigating the role of sugar consumption on diabetes risk, which usually find that effect sizes are substantially attenuated after controlling for BMI [39, 48]. At the same time, evidence for independent causal effects of free sugars on diabetes risk has so far been limited. Lean and Te Morenga [42] therefore conclude that associations between sugar consumption and type 2 diabetes are mainly mediated through overweight and obesity. Given the role of free sugars in promoting weight gain (discussed in the previous section), sugar consumption above recommended levels must be considered a risk factor for the development of type 2 diabetes.

19.3.2.3 Cardiovascular Disease (CVD)

Dietary sugars have also been implicated in the development of cardiovascular disease. The evidence for causal effects of dietary factors on cardiometabolic diseases (based on Bradford-Hill criteria) was assessed in a 2017 systematic review by the Nutrition and Chronic Diseases Expert Group, which concluded that high intake of sugar-sweetened beverages had harmful effects over and above their contribution to unhealthy weight gain [49]. This assessment is corroborated by a number of other recent reviews and meta-analyses [6, 50–52].

Excessive consumption of dietary sugars is associated with increased blood pressure and increased levels of serum lipids [51]. Fructose-containing sugars may cause lipid accumulation in the liver through de novo lipogenesis, as well as decreased insulin sensitivity [52]. These mechanisms are independent of the effects of sugar on body weight, which in itself is a risk factor for CVD [6]. Further research is, however, needed to confirm these potential mechanisms and to assess the effects of free sugars contained in solid foods.

19.4 Patterns and Trends in Free Sugars Consumption

Sugar is cheap and widely available. World sugar production is estimated to reach 178.9 million tonnes in 2018/2019, with India as the largest sugar producing country, followed by Brazil, the EU, Thailand, China, and the USA (◘ Fig. 19.2) [53].

The global consumption of sugar amounted to 173.6 million metric tonnes in 2018/2019 and is projected to increase to 198 million metric tonnes in 2027. India's growing economy has led the country to a record on sugar consumption, amounting to approximately 27.5 million metric tonnes, which represents a 4% increase over the last 5 years. Conversely, for the last few years

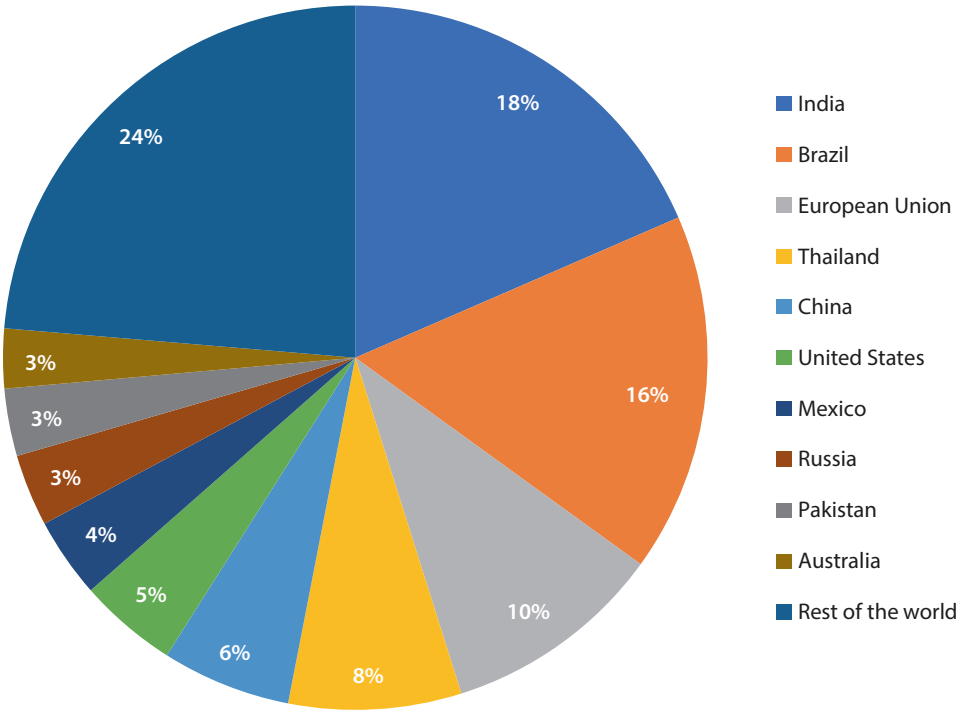


Fig. 19.2 World sugar production. (Data extracted from the USDA Yearbook, May 2019) [53]

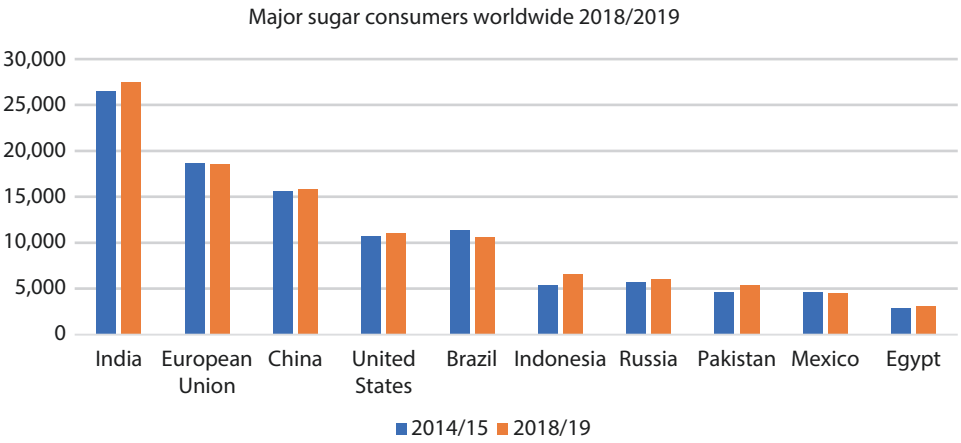


Fig. 19.3 Major sugar consumers in the world 2018/2019. (Data extracted from the USDA Yearbook, May 2019) [53]

the EU's sugar consumption has stalled due to changes in consumer preferences and product reformulations by the food industry (Fig. 19.3) [53].

According to the FAO Food Outlook 2019, there has been no growth in total and per capita consumption in high-income countries [54]. Moreover, levels of sugar intake are projected to decline at the individual level. For example, in the United States sugar intake by individuals aged 2 years and over decreased by 15 grams per day over the last 10 years [55]. Likewise, between 2008/2009 and 2016/2017, the UK's sugar consumption fell by 2.4 and 1.2 percentage points in children and adults, respectively [56]. Consumers' attitudes towards sugar in these countries have changed for several reasons, including increasing health awareness, dietary preferences, the introduction of a sugar tax, and nutritional commitments from industry [57].

Despite these reductions, the mean intake of free sugars in high-income countries still far exceeds the levels recommended by the WHO and local governments. Moreover, despite the increasing public interest in reducing sugar consumption in high-income countries, inequalities persist. Children living in countries with larger social inequalities in health are more likely to report higher average sugar consumption. UNICEF reports that the relationship between relative inequalities and average levels of unhealthy eating in children (defined as excess consumption of sugary foods and beverages) is strong. Although inequalities in sugar intake between more and less disadvantaged children have

decreased in most EU and OECD countries, in countries such as Belgium, Romania, Slovakia and Turkey bottom-end inequality (the gap between children at the bottom and those in the middle) has increased by 2 or more percentage points since 2002 [58].

In the context of large and abundant supply and falling prices, flatlining or falling sugar consumption in high-income countries has contributed to the industry shifting their operations towards low- and middle-income countries, where consumption is rising [3]. Sugar consumption is currently rising in Latin America and the Caribbean. In 2015, Argentina, Colombia, and Peru had the highest values, whilst Brazil and Chile had the lowest values of total sugar intake [59]. The increasing demand for processed food products, sugar-rich confectionary and soft drinks will increase the sugar consumption in low- and middle-income countries with the most significant contributions occurring in Asia (60%) and Africa (25%), where levels of consumption are currently low. Thus, it is expected that India, China, Indonesia, Pakistan, Egypt and several Sub-Saharan countries will experience the largest increases in sugar consumption over the next 10 years [54].

Regardless of the level of development and economy in a given country, evidence shows that high sugar consumption is associated with lower socioeconomic status [60–62]. Diets rich in sugar are cheaper and more energy-dense. Thus, people living in poverty tend to adopt dietary patterns high in sugar to satisfy hunger. Food prices might be a barrier in the adoption of healthier diets by lower socioeconomic groups. Measures such as pricing interventions, food assistance programs, taxations and dietary guidelines may help in the adoption of healthier diets.

19.5 Social and Commercial Determinants of Sugar Consumption

Often the term 'lifestyle' is used to describe various behaviours that are associated with disease risk. Smoking, drinking excess amounts of alcohol, lack of exercise, drug misuse, unsafe sex and eating poor quality diets are all collectively labelled as 'lifestyles', a term that suggests that these behaviours are rational and freely made choices made by individuals. This reductionist and simplistic view, still very dominant in clinical disciplines, totally fails to acknowledge that all these behaviours are actually influenced by a complex array of interacting biological, psychological, social, environmental, economic and political factors – the social determinants of health [63]. In broad terms, the conditions and context in which people live their daily lives influence and ultimately determine the behaviours and actions taken [64]. Health behaviours are therefore not merely rational choices, freely and equally available to all. Instead they are a reflection of broader society and the underlying driving forces that influence and ultimately dictate the options open to people. A social determinants approach provides a valuable lens to understand patterns of disease in the population and health inequalities.

The consumption of sugars provides a perfect example to illustrate the above concepts. Busy dental clinicians working in health care systems that prioritise an interventionist approach and the treatment of disease are aware of the importance of reducing sugars consumption in terms of caries prevention, but with limited time available and little incentive, merely provide simple information on sugar reduction in the vain hope that this will help change their patients' 'bad' behaviours. The evidence suggests that at best, chairside health education will work only in the short term and only amongst middle class and affluent patients who are able and motivated to change their habits [65–68]. The strategy of only providing chairside advice to reduce a patient's sugar consumption is a failure because such a simple approach totally and utterly fails to acknowledge and address the underlying factors influencing and determining sugar consumption. The amount and pattern of sugars consumed by an individual are influenced by a complex web of interacting factors. At a macro level, an array of policies (e.g. agricultural, economic, commercial, housing, town planning, employment, development) will influence the production, price, affordability and availability of sugars, whereas socio-cultural norms in society will determine the acceptability and desirability of sugar to different population groups. At a meso level, the promotion, marketing and advertising strategies of the food industry will influence consumer behaviours, and the quality and clarity of food labelling will help or hinder food and drink choices. The availability and selection of food and drink options in settings such as schools, hospitals, workplaces, and leisure facilities will again largely determine the options and choices available. The design and nature of the home environment, in particular access to adequate cooking and storage facilities, will influence individuals' and families' ability to prepare and cook healthier foods at home. Foods and drinks, and in particular sugary 'treats', are heavily influenced by family and social relationships – for example intergenerational conflict often occurs in families (parents versus grandparents) over the acceptability of giving confectionary as a token of affection and love to young children. Finally, at the micro level, an individuals' knowledge (e.g. 'Are natural sugars in honey and fruit juices harmful or not?'), cooking skills and their ability and confidence to prepare healthier meals and snacks will influence how much sugar they consume. Psychological and biological factors also have an influence – when under stress and experiencing anxi-

ety, people often resort to 'comfort' eating and sugary items are particularly desired as a coping mechanism. Innate preference for sugar at birth highlights the biological processes influencing taste preference in early life, although evidence indicates that sweet preference is modifiable – the more sugar an infant is given, the more they will demand [69].

Over the last 20 years, health policy and public health practitioners have increasingly recognised the social determinants of health and the urgent need to address the upstream economic, political and environmental driving influences on population health and socio-economic inequalities in health. More recently, attention has also focused on the commercial determinants of health, an analysis directly pertinent to sugar and the promotion of population oral health [3]. The commercial determinants of health have been defined as 'strategies and approaches used by the private sector to promote products and choices that are detrimental to health' [70]. Corporate strategies employed by transnational corporations that can negatively influence health include marketing, promotion and advertising to enhance the desirability and acceptability of products and increase profit margins, lobbying (both direct and indirect) to influence policy and legislation in favour of corporate goals, and lastly by using corporate responsibility and citizenship deals to enhance industry social acceptability via activities such as sponsorship of sporting and cultural events and health care initiatives. The tobacco and alcohol industries are the most obvious corporations that threaten public health but increasingly attention is also focusing on food manufacturers, and in particular, the sugar industry.

The global sugar industry has significant economic, political and policy influence. Coca-Cola and PepsiCo, the two largest soft drinks companies, dominate the global soft drinks market and have combined revenues in excess of US$100 billion, greater than many medium-sized countries [9]. Economic success readily translates into political and policy influence. For example in the United States, Coca-Cola, PepsiCo and the American Beverage Association collectively spent over US$110 million lobbying at the federal level between 2009 and 2015 [71]. At the international level, the sugar industry has heavily lobbied policy decisions at the World Health Organisation and even threatened to get US funding support for the WHO removed [72]. The sugar industry also spends vast amounts of money on advertising and marketing their products in an increasingly sophisticated and targeted manner. In 2013, US soft drinks companies spent over US$850 million on advertising sugary drinks [73]. The industry focus is increasingly moving away from high-income countries where sales are static or even falling to emerging markets in low- and middle-income countries where significant growth is expected. For example, Coca-Cola has outlined plans to invest more than US$4 billion in China and US$12 billion on marketing their products across Africa [9].

In recent years, evidence has emerged on the range of tactics used by the global sugar industry to influence public health policies that might threaten their sales and profits. Key tactics include discrediting research and policy recommendations that highlight the role of sugars in the development of disease, and instead shifting the policy focus onto other factors such as fluorides and physical activity, enlisting the support of politicians to block policies either directly or indirectly, and funding supposedly independent think-tanks to gain influence and access to key policy makers [74, 75].

19.6 Policy Action to Reduce Sugar Consumption

Despite of the best efforts of the sugar industry to cause confusion and controversy to divert attention away from sugar as a public health priority, it is very important to acknowledge the overwhelming international scientific evidence on the role of free sugars for both dental caries and weight gain [12, 13]. Consensus national and international guidelines have very clearly defined agreed recommendations on the urgent need to reduce free sugar consumption [5, 17]. However as outlined above, in most high- and middle-income countries, free sugar consumption far exceeds the current recommendations to keep this below 10% of total dietary energy, across the entire population from early childhood to older age. In many low-income countries but particularly in Africa, maintaining the relatively low levels of free sugar consumption seen currently is also a key policy recommendation. Although the consensus recommendations are now very clear, the major policy challenge is how to achieve them.

From a public health perspective, although individual dietary advice and support delivered by health professionals is important, to significantly reduce free sugar consumption at a population level requires a complementary range of downstream, midstream and upstream measures acting together across the relevant organisations, agencies and sectors involved [8, 76]. There is a surprisingly sparse literature on dietary interventions delivered by dental professionals working in a clinical setting [77]. Dental professionals need to be trained and have appropriate resources to deliver effective dietary advice to their patients. The information provided must be based on up-to-date nutritional science and in line with general nutritional guidelines to avoid conflicting and contradictory diet messages being delivered. Effective dietary advice requires good communication skills to collect an accurate diet history and to provide tailored advice and support to patients while

recognising their unique individual and social circumstances and ability to change their behaviour.

Midstream strategies principally focus on policies and actions to reduce free sugars through joint action with retailers, public sector organisations and other businesses. For example, restrictions on supermarkets and other retailers displaying and selling high-sugar snack foods and drinks at checkouts and instead replacing them with alternative healthier options is an important measure to reduce pressure on parents to buy sugary items. Many supermarkets also have special price promotions ('buy one, get one free' offers) that frequently give major discounts on sugary products such as soft drinks and confectionary. Working with retailers to change these pricing promotions to instead discount healthier choices is particularly important for lower-income households with tight budgets. Portion sizes of soft drinks and sugary snacks have steadily increased in recent years – action is needed to reduce the quantities of these items sold in cinemas and other public spaces. Many public sector organisations including hospitals and clinics have shops, cafes and vending machines on their premises, which often sell very unhealthy foods and drinks to patients, visitors and staff. In several countries, action is now being taken to stop selling sugary products in clinical settings as part of a drive to become more of a health-promoting environment. Mandatory food guidelines in preschools and schools to improve the overall nutritional quality of meals and snacks served to children should include tighter restrictions on free sugars.

Moving further upstream requires legislation, regulation and national policy development to drive substantial reductions in free sugar consumption through action on tackling the availability, price and marketing of sugar. An important approach is working with industry to reformulate processed products to reduce their free sugar content. A similar approach has already been successfully used to reduce the salt content of many savoury and processed foods. The reformulation of soft drinks, biscuits, cakes and other processed foods could have a significant effect in reducing the overall consumption of free sugars in the population. This does not require the consumers to change their behaviour – instead industry makes the healthy changes to their products. An added advantage of this approach is that it can be carried out incrementally so that consumers are unaware of the gradual reduction in sugar content. Government taxes or levies on sugary products are becoming increasingly popular, with over 50 countries now introducing price changes on sugar-sweetened beverages. Evidence suggests that at least a 20% increase in price is needed to have an impact on sales and consumption of sugary products [78]. Evaluations of the pricing policies in Mexico have shown that following their introduction, sales and consumption of sugary drinks have reduced, as have levels of overweight [79]. In the United Kingdom, a sugar levy was introduced in 2018, and its immediate effect was industry reformulating their products to reduce their sugar content to avoid price increases [80]. Another very important upstream policy is the need for tighter regulation and improvement in food labelling to enable consumers to make informed choices. Currently, the labelling of free sugars is confusing, complex and inconsistent. Red, amber and green traffic light systems are much simpler and easy for consumers to understand [81]. Finally, the marketing strategies to promote the sales of sugary foods and drinks, which often specifically target children, need much tighter control. Advertising standards authorities need to restrict the largely uncontrolled marketing and promotion strategies used by the sugar industry. For example, in several countries a watershed has been introduced, which prohibits television adverts that target children being shown before 9 pm.

19.7 Conclusion

Sugar is a powerful commercial determinant of oral and general health. Reducing the consumption of free sugars is therefore not only a priority for promoting oral health but also for the prevention of obesity and the chronic diseases related to it. The sugar industry is a global player with vested interests, and it is most worrying that low-income countries are now being targeted. If the industry's influence is not countered through regulation, rises in sugar consumption will be followed by rises in the prevalence of NCDs. Successful tobacco control policies have shown the way – taxation and regulation are powerful instruments against corporate interests that threaten public health. Governments must use them.

References

1. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, Murray CJL, Marcenes W. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96(4):380–7.
2. Watt RG, Daly B, Allison P, Macpherson LMD, Venturelli R, Listl S, Weyant RJ, Mathur MR, Guarnizo-Herreño CC, Celeste RK, Peres MA, Kearns C, Benzian H. Ending the neglect of global oral health: time for radical action. Lancet. 2019;394(10194):261–72.
3. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, Listl S, Celeste RK, Guarnizo-Herreño CC, Kearns C, Benzian H, Allison P, Watt RG. Oral diseases: a global public health challenge. Lancet. 2019;394(10194):249–60.
4. Popkin BM, Hawkes C. The sweetening of the global diet, particularly beverages: patterns, trends and policy responses for diabetes prevention. Lancet Diabetes Endocrinol. 2016;4(2):174–86.

5. WHO. Guideline: sugars intake for adults and children. Geneva: World Health Organization; 2015.
6. Malik VS, Popkin BM, Bray GA, Després J-P, Hu FB. Sugar sweetened beverages, obesity, type 2 diabetes and cardiovascular disease risk. Circulation. 2010;121(11):1356–64.
7. Watt RG, Sheiham A. Integrating the common risk factor approach into a social determinants framework. Community Dent Oral Epidemiol. 2012;40(4):289–96.
8. Stuckler D, McKee M, Ebrahim S, Basu S. Manufacturing epidemics: the role of global producers in increased consumption of unhealthy commodities including processed foods, alcohol, and tobacco. PLoS Med. 2012;9(6):e1001235.
9. Nestle M. Soda politics: taking on big soda (and winning). Oxford: Oxford University Press, USA; 2015.
10. Cummings JH, Stephen AM. Carbohydrate terminology and classification. Eur J Clin Nutr. 2007;61 Suppl 1:S5–18.
11. Moynihan P, Makino Y, Petersen PE, Ogawa H. Implications of WHO Guideline on Sugars for dental health professionals. Community Dent Oral Epidemiol. 2018;46(1):1–7.
12. Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ. 2013;346:e7492.
13. Moynihan PJ, Kelly SAM. Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines. J Dent Res. 2014;93(1):8–18.
14. Sheiham A, James WP. Diet and dental caries: the pivotal role of free sugars reemphasized. J Dent Res. 2015;94(10):1341–7.
15. Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2003;1:CD002278.
16. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S, Grade Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
17. SACN. Carbohydrates and health. London: Scientific Advisory Committee on Nutrition; 2015.
18. WHO. Diet, nutrition and the prevention of chronic diseases. Geneva: WHO; 2003.
19. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4):309–16.
20. Moynihan P, Petersen PE. Diet, nutrition and the prevention of dental diseases. Public Health Nutr. 2004;7(1a):201–26.
21. Tham R, Bowatte G, Dharmage SC, Tan DJ, Lau MXZ, Dai X, Allen KJ, Lodge CJ. Breastfeeding and the risk of dental caries: a systematic review and meta-analysis. Acta Paediatr. 2015;104:62–84.
22. Public Health England. Breastfeeding and dental health. 2019. Available from: http://www.gov.uk/government/publications/breastfeeding-and-dental-health/breastfeeding-and-dental-health. Accessed 23 July 2019.
23. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475–90.
24. World Health Organization. Global strategy for infant and young child feeding. Geneva: WHO; 2003. http://www.who.int/nutrition/publications/infantfeeding/9241562218/en/.
25. Bernabé E, Vehkalahti MM, Sheiham A, Lundqvist A, Suominen AL. The shape of the dose-response relationship between sugars and caries in adults. J Dent Res. 2016;95(2):167–72.
26. Van der Velden U, Kuzmanova D, Chapple ILC. Micronutritional approaches to periodontal therapy. J Clin Periodontol. 2011;38(s11):142–58.
27. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000. 2013;62(1):59–94.
28. Lula ECO, Ribeiro CCC, Hugo FN, Alves CMC, Silva AAM. Added sugars and periodontal disease in young adults: an analysis of NHANES III data. Am J Clin Nutr. 2014;100(4):1182–7.
29. Chapple ILC, Bouchard P, Cagetti MG, Campus G, Carra M-C, Cocco F, Nibali L, Hujoel P, Laine ML, Lingström P, Manton DJ, Montero E, Pitts N, Rangé H, Schlueter N, Teughels W, Twetman S, Van Loveren C, Van der Weijden F, Vieira AR, Schulte AG. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. J Clin Periodontol. 2017;44(S18):S39–51.
30. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. Am J Clin Nutr. 2006;84(2):274–88.
31. Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr. 2013;98(4):1084–102.
32. Olsen NJ, Heitmann BL. Intake of calorically sweetened beverages and obesity. Obes Rev. 2009;10(1):68–75.
33. Woodward-Lopez G, Kao J, Ritchie L. To what extent have sweetened beverages contributed to the obesity epidemic? Public Health Nutr. 2010;14(3):499–509.
34. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. Am J Public Health. 2007;97(4):667–75.
35. Luger M, Lafontan M, Bes-Rastrollo M, Winzer E, Yumuk V, Farpour-Lambert N. Sugar-sweetened beverages and weight gain in children and adults: a systematic review from 2013 to 2015 and a comparison with previous studies. Obes Facts. 2017;10(6):674–93.
36. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. PLoS Med. 2014;10(12):e1001578.
37. Wang M, Yu M, Fang L, Hu R-Y. Association between sugar-sweetened beverages and type 2 diabetes: a meta-analysis. J Diabetes Investig. 2015;6(3):360–6.
38. Malik VS, Popkin BM, Bray GA, Després J-P, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes. Diabetes Care. 2010;33(11):2477.
39. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ (Clinical research ed). 2015;351:h3576.
40. Neuenschwander M, Ballon A, Weber KS, Norat T, Aune D, Schwingshackl L, Schlesinger S. Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. BMJ. 2019;366:l2368.
41. Basu S, Yoffe P, Hills N, Lustig RH. The relationship of sugar to population-level diabetes prevalence: an econometric analysis of repeated cross-sectional data. PLoS One. 2013;8(2):e57873.
42. Lean MEJ, Te Morenga L. Sugar and type 2 diabetes. Br Med Bull. 2016;120(1):43–53.
43. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. N Engl J Med. 2013;369(10):954–64.
44. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev. 2007;29(1):115–28.

45. Forouhi NG, Misra A, Mohan V, Taylor R, Yancy W. Dietary and nutritional approaches for prevention and management of type 2 diabetes. BMJ. 2018;361:k2234.
46. Hu FB. Metabolic consequences of obesity. In: Obesity epidemiology. Oxford: Oxford University Press; 2008.
47. Merlotti C, Morabito A, Pontiroli AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. Diabetes Obes Metab. 2014;16(8):719–27.
48. Greenwood DC, Threapleton DE, Evans CEL, Cleghorn CL, Nykjaer C, Woodhead C, Burley VJ. Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose–response meta-analysis of prospective studies. Br J Nutr. 2014;112(5):725–34.
49. Micha R, Shulkin ML, Peñalvo JL, Khatibzadeh S, Singh GM, Rao M, Fahimi S, Powles J, Mozaffarian D. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). PLoS One. 2017;12(4):e0175149.
50. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, De Henauw S, Michels N, Devleesschauwer B, Schlesinger S, Schwingshackl L. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2019;59(7):1071–90.
51. Te Morenga LA, Howatson AJ, Jones RM, Mann J. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr. 2014;100(1):65–79.
52. Stanhope KL, Goran MI, Bosy-Westphal A, King JC, Schmidt LA, Schwarz JM, Stice E, Sylvetsky AC, Turnbaugh PJ, Bray GA, Gardner CD, Havel PJ, Malik V, Mason AE, Ravussin E, Rosenbaum M, Welsh JA, Allister-Price C, Sigala DM, Greenwood MRC, Astrup A, Krauss RM. Pathways and mechanisms linking dietary components to cardiometabolic disease: thinking beyond calories. Obes Rev. 2018;19(9):1205–35.
53. USDA. Sugar: World Markets and Trade United State Department of Agriculture. Economic Research Service. 2019. [Accessed].
54. FAO. Food Outlook- Biannual report on global food markets. Rome. 2019. 40–45.
55. Bowman S, Clemens JC, Friday JE, Lynch KL, LaComb RP, Moshfegh AJ. Food Patterns equivalents intakes by Americans: what we eat in America, NHANES 2003–2004 and 2013–2014 Food Surveys Research Group. 2017. [Accessed]. Available from: http://www.ars.usda.gov/Services/docs.htm?docid=19476.
56. PHE. National diet and nutrition survey. Years 1 to 9 of the Rolling Programme (2008/2009–2016/2017): Time trend and income analyses. 2019.
57. OECD/FAO. Sugar. OECD-FAO Agricultural Outlook 2018-2027. Paris/FAO, Rome: OECD Publishing; 2018. p. 144.
58. UNICEF. Fairness for children: a league table of inequality in child well-being in rich countries, Innocenti Report Card 13. Florence: UNICEF Office of Research – Innocenti; 2016.
59. Fisberg M, Kovalskys I, Gómez G, Rigotti A, Sanabria LYC, García MCY, Torres RGP, Herrera-Cuenca M, Zimberg IZ, Koletzko B, Pratt M, Aznar LAM, Guajardo V, Fisberg RM, Sales CH, Previdelli ÁN, Group ES. Total and added sugar intake: assessment in eight Latin American countries. Nutrients. 2018;10(4):389.
60. Han E, Powell LM. Consumption patterns of sugar sweetened beverages in the United States. J Acad Nutr Diet. 2013;113(1):43–53.
61. Mazarello Paes V, Hesketh K, O'Malley C, Moore H, Summerbell C, Griffin S, van Sluijs EMF, Ong KK, Lakshman R. Determinants of sugar-sweetened beverage consumption in young children: a systematic review. Obes Rev. 2015;16(11):903–13.
62. Bolt-Evensen K, Vik FN, Stea TH, Klepp K-I, Bere E. Consumption of sugar-sweetened beverages and artificially sweetened beverages from childhood to adulthood in relation to socioeconomic status - 15 years follow-up in Norway. Int J Behav Nutr Phys Act. 2018;15(1):8–8.
63. Commission on Social Determinants of Health. Closing the gap in a generation. Health equity through action on the social determinants of health. Geneva: World Health Organization; 2008.
64. Sheiham A. Improving oral health for all: focusing on determinants and conditions. Health Educ J. 2000;59(4):351–63.
65. Kay EJ, Locker D. Is dental health education effective? A systematic review of current evidence. Community Dent Oral Epidemiol. 1996;24(4):231–5.
66. Yevlahova D, Satur J. Models for individual oral health promotion and their effectiveness: a systematic review. Aust Dent J. 2009;54(3):190–7.
67. Schou L, Wight C. Does dental health education affect inequalities in dental health? Community Dent Health. 1994;11(2):97–100.
68. Qadri G, Alkilzy M, Franze M, Hoffmann W, Splieth C. School-based oral health education increases caries inequalities. Community Dent Health. 2018;35(3):153–9.
69. Ventura Alison K, Worobey J. Early influences on the development of food preferences. Curr Biol. 2013;23(9):R401–8.
70. Kickbusch I, Allen L, Franz C. The commercial determinants of health. Lancet Glob Health. 2016;4(12):e895–6.
71. Center for Science in the Public Interest. Big soda vs. public health: how the industry opens its checkbook to defeat health measures. Washington, DC: CSPI; 2015.
72. Boseley S. Political context of the World Health Organization: sugar industry threatens to scupper the WHO. Int J Health Serv. 2003;33(4):831–3.
73. Rudd Center for Food Policy and Obesity. Sugary drink facts 2014: some progress but much room for improvement in marketing to youth. 2014. http://www.sugarydrinkfacts.org/resources/sugarydrinkfacts_report.pdf.
74. Kearns CE, Glantz SA, Schmidt LA. Sugar industry influence on the scientific agenda of the National Institute of Dental Research's 1971 National Caries Program: a historical analysis of internal documents. PLoS Med. 2015;12(3):e1001798.
75. O'Connor A. Coca-Cola funds scientists who shift blame for obesity away from bad diets. New York Times, 09/08/2015. 2015. https://well.blogs.nytimes.com/2015/08/09/coca-cola-funds-scientists-who-shift-blame-for-obesity-away-from-bad-diets/.
76. Public Health England. Sugar reduction: responding to the challenge. London: PHE; 2014. http://www.gov.uk/government/publications/sugar-reduction-responding-to-the-challenge.
77. Harris R, Gamboa A, Dailey Y, Ashcroft A. One-to-one dietary interventions undertaken in a dental setting to change dietary behaviour. Cochrane Database Syst Rev. 2012;3:CD006540.
78. Public Health England. Sugar reduction: the evidence for action. London: PHE; 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470179/Sugar_reduction_The_evidence_for_action.pdf.
79. Barrientos-Gutierrez T, Zepeda-Tello R, Rodrigues ER, Colchero MA, Rojas-Martinez R, Lazcano-Ponce E, Hernandez-Avila M, Rivera-Dommarco J, Meza R. Expected population weight and diabetes impact of the 1-peso-per-litre tax to sugar sweetened beverages in Mexico. PLoS One. 2017;12(5):e0176336.
80. Public Health England. Sugar reduction and wider reformulation programme: report on progress towards the first 5% reduction and next steps. London: PHE; 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/709008/Sugar_reduction_progress_report.pdf.
81. Malam S, Clegg S, Kirwan S, McGinigal S. Comprehension and use of UK nutrition signpost labelling schemes. London: Food Standards Agency; 2009.

Oral Health-Related Quality of Life

Georgios Tsakos and Finbarr Allen

Contents

20.1 Introduction – 320

20.2 The Concept of Quality of Life and Relevant Theoretical Frameworks – 320

20.3 OHRQoL Measures That Stood the Test of Time – 322

20.4 Measurement Properties and Key Characteristics – 323

20.5 How Have They Been Used? Applications – 325

20.6 Issues in OHRQoL Research: (Mis)interpretation – 326

20.7 What Way Forward? – 327

Appendix: Comprehensive List of Oral Health-Related Quality of Life Measures (■ Tables 20.3, 20.4, and 20.5) – 328

References – 330

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_20

Learning Objectives

- Understand the concept of oral health-related quality of life
- Be familiar with the frameworks used to shape subjective health status measurement
- Be familiar with the currently available oral health-related quality of life measures and their measurement properties
- Be able to choose a measure that is context-appropriate
- Get a critical insight into their potential applications and interpretation

20.1 Introduction

In the last decades, there has been an increasing interest about subjective perceptions of health (and oral health), and this has led to the development of a plethora of subjective measures of health and quality of life. Indeed, there is now an extensive volume of literature reporting on the subjective oral health of populations and the impact the oral conditions have had on their quality of life. While the focus of the oral health research community was initially on measures for adults and also for the elderly, broadly similar measures for children and adolescents have also been developed in the last 15 years. Most of those measures have been validated, but only a few of them have stood the test of time, adapted for use in different settings and cultures and are still being used today. The theoretical frame of reference for subjective health status measurement has also shifted from measurement of disease and disability to health and function, and oral health is somewhat lagging in developing new measures based on this new paradigm.

20.2 The Concept of Quality of Life and Relevant Theoretical Frameworks

Conceptually, this field of research is rooted in the proven inadequacy of the biomedical model and the emergence (already since many decades) of the biopsychosocial model of health to guide measurement of health outcomes [1]. Health outcome measurement under the biomedical model was traditionally focused on survival periods, toxicity and biochemical indicators, thereby using solely disease-related clinical data and following a reductionist approach based on pathology and tissue damage. However, physiologic measures often correlate poorly with functional ability and well-being, and people with similar clinical status often have dramatically different perceptions about their health [2].

The dominance of chronic diseases in the epidemiological profile of populations has further highlighted the considerable limitations of the biomedical model, as the emphasis has shifted from the absence of disease towards managing comorbidities so that people can maintain an acceptable level of health and enjoy good quality of life. In that respect, more value is placed on self-reports, and health outcomes should incorporate both medical and patient's perspectives, encompassing physical health and functioning, social functioning, psychological and emotional well-being [1]. Quality of life was the term used to capture 'the individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' [3].

In addition to being important for assessing the functional and psychosocial impacts of chronic diseases, subjective outcome measures of health and quality of life tend to be more easily comprehensible and therefore also more policy relevant. For example, advocacy and engagement with policy makers about oral health may be streamlined through highlighting the proportion of people with toothache experience or with difficulty eating due to their oral conditions rather than put forward the statistics about key clinical disease indicators (such as the mean DMFT score). Furthermore, subjective perceptions and relevant health outcomes are key underlying constructs in the provision of services. Typically, this was recognized even in high-profile cases, such as the court case for hip replacement and provision of care that was handled by the European Court of Justice [4] (► Box 20.1).

Box 20.1 European Court of Justice (Luxembourg, 2006): Ruling on Yvonne Watts, Aged 75, from Bedford (Funding of Hip Replacement Abroad Because of 'Undue Delay' in NHS in Britain)

Treatment provision determined by 'an objective medical assessment of the patient's medical condition, the history and probable course of her illness, the degree of pain she is in and/or the nature of her disability at the time' [4]. If the patient qualifies on that basis, then it should be available within the clinically necessary time at NHS expense, whether in this country or abroad, in a public or a private hospital.

In oral health, a seminal paper by Cohen and Jago [5] discussed the changing concepts of health and models of disease and put forward the case for adding a dimension of social impact to the clinical indicators. Other early conceptual and empirical contributions to the literature provided the rationale for development of subjective outcomes of oral health and quality of life [6–9]. Indeed, it has been the conceptual framework for measuring oral health that was proposed by Locker [7] that stimulated

empirically based development of key relevant measures in the 1990s, such as the Oral Health Impact Profile (OHIP) and the Oral Impacts on Daily Performances (OIDP). Locker's conceptual framework was adapted from the International Classification of Impairments, Disabilities and Handicaps (ICIDH) framework and followed a linear model from disease to impairment and then to disability and handicap (Fig. 20.1).

Interestingly, the ICIDH has been superseded as a conceptual framework by the International Classification of Functioning, Disability and Health (ICF), but the aforementioned measures have continued to be used extensively and consistently to provide evidence about the impact of oral conditions on the quality of life of people and populations.

While these outcome measures have largely remained unchanged, their terminology has been characterized by less stability, thereby implying lack of clarity about the constructs covered and the way they are measured [10]. At different periods, they have been termed sociodental indicators (initially), subjective oral health status measures, oral health outcome measures, oral health-related quality of life (OHRQoL) measures, as well as quality of life measures. These terms are used almost interchangeably and treated as reflecting the same constructs, which though are rarely defined in a precise way. This is by no means a debate that characterized only the oral health field, and similar variation in terms was also seen in general health, indicating lack of conceptual clarity and therefore hindering appropriate measurement [11]. In an effort to overcome the terminology confusion, Fitzpatrick et al. [12] suggested that they are called patient-based outcome measures as they reflect what patients have to say about their health. Irrespective of the terminology, these are measures of the extent that health status and conditions disrupt normal social-role functioning and bring about major changes in behaviour [13]. In essence, they are subjective indicators that provide information on the impact of oral disorders and conditions, and the perceived need for oral health care. Their use should be seen as complementary to clinical measures rather than substituting them.

An important conceptual contribution towards incorporating subjective outcomes into a composite framework was made by Wilson and Cleary [14]. Their model contains biological and physiological variables, as well as symptoms, which reflect the more traditional approach of the biomedical model, while it also focuses on functioning, general health perceptions and overall quality of life, thereby giving prominence to subjective perceptions and reflecting the constructs that characterize the biopsychosocial model of health. The model postulated specific causal relationships that link traditional clinical variables to subjective measures of quality of life (Fig. 20.2).

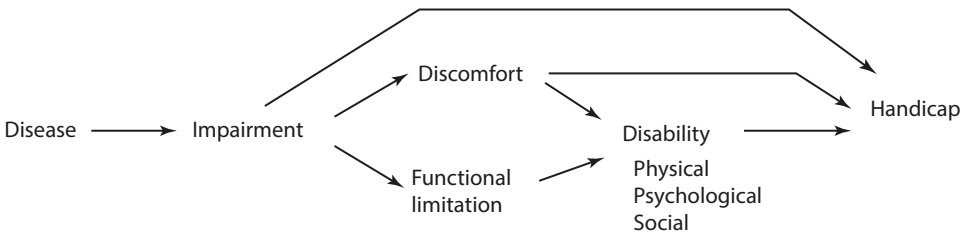


Fig. 20.1 Conceptual framework for oral health [7]

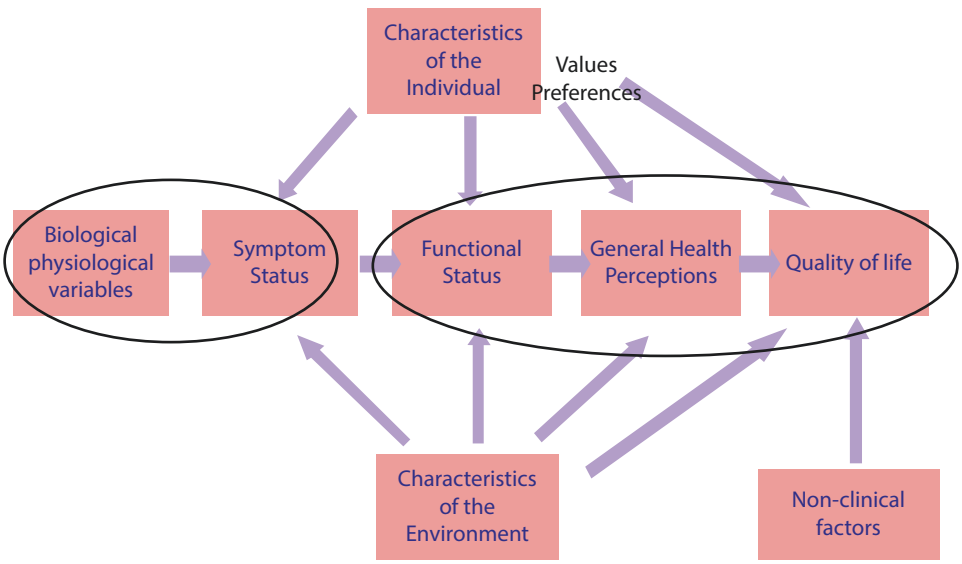


Fig. 20.2 Outcome measures model [14] [circles added by authors of this chapter to indicate the main concepts reflecting the biomedical model –on the left, and the concepts primarily reflecting the biopsychosocial model – on the right]

This move towards a more inclusive and less disease-based model of health has also been reflected in the proposed new definition of oral health that was adopted by the World Dental Federation – FDI [15]. The biopsychosocial model provides the underlying set of constructs for this new definition that places the social determinants of health and subjective oral health outcomes in a central role to provide a comprehensive picture of oral health. This is reflected in recent work undertaken by the FRDI and the Internatinal Consortium for Health Outcomes Measurement (ICHOM) for the determination of a set of oral health outcomes for adults, with subjective outcomes having a prominent role [16]. This oral health outcomes set is expected to be relevant for clinical practice, as well as policy/advocacy.

20.3 OHRQoL Measures That Stood the Test of Time

A number of composite 'OHRQoL' measures have been developed and validated for use among general populations and also among dental patients. Following a consensus conference held at the University of North Carolina in 1996, a publication contained many of the then newly developed measures [17]. These were all measures developed for adults as children were initially not given due attention, possibly due to issues around measurement of more abstract constructs (and 'OHRQoL' would definitely fit under this classification, no matter which definition one would follow) associated with their developmental stage. Another possible reason is simply that researchers may have expected a lifetime of experience of oral conditions to have a higher level of impact on people's quality of life; therefore, selecting adults (and older adults) would be more relevant as a starting point. However, a few years later OHRQoL measures for children have emerged in the relevant literature, usually with a relatively similar content as those for adults.

The emergence of such measures was gradually welcomed and over the years they have been seen, without any real justification, as the solution to many (or even all) of the issues around outcome measurement in oral health. However, they are subject to many limitations both conceptually and from a more technical point of view [10, 18]. Indeed, many of the OHRQoL measures included in the North Carolina conference publication [17] have hardly been used further than their initial development and validation. It is worth clarifying that these first measures were generic in nature, i.e. they were not linked to specific oral conditions. This has the advantage of being applicable generally and therefore potentially relevant to compare health outcomes across oral conditions and populations. However, it is less clear as to whether they may be relevant for some oral conditions or responsive to clinical status changes. On the other hand, a number of condition-specific OHRQoL measures have been subsequently developed with the expectation that they would be more relevant and easily accepted by patients suffering from a particular oral condition and also responsive to clinical changes, though their application and comparability is by definition more limited. Table 20.1 presents some of the more widely used OHRQoL measures, while a more comprehensive list of generic and condition-specific OHRQoL measures is presented as an Appendix.

Three of these initial OHRQoL measures (OHIP, OIDP and GOHAI) have stood the test of time and are still widely used, with the OHIP-14 being the most widely reported measure [18]. The OHIP was firstly developed as a 49-item questionnaire to assess the frequency of oral impacts, in relation to the following seven domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap [19]. Soon after, the need for a shorter questionnaire that could be more easily applicable in clinical practice and epidemiology led to the development of OHIP-14 [20] that retained two questions for each of the seven domains.

The Oral Impacts on Daily Performances (OIDP) assesses both the frequency and severity of the impacts

Table 20.1 Examples of widely used oral health-related quality of life measures

Authors	OHRQoL measure
Measures for adults	
Slade and Spencer [19]	Oral Health Impact Profile (OHIP)
Slade [20]	Oral Health Impact Profile-14 (OHIP-14)
Adulyanon and Sheiham [21]; Tsakos et al. [22]	Oral Impacts on Daily Performances (OIDP)
Atchison and Dolan [23]	Geriatric/General Oral Health Assessment Index (GOHAI)
Measures for children	
Jokovic et al. [24]	Child Perceptions Questionnaire / CPQ
Gherunpong et al. [25]	Child Oral Impacts on Daily Performances (C-OIDP)
Pahel et al. [26]	Early Childhood Oral Health Impact Scale (ECOHIS)
Broder et al. [27]	Child Oral Health Impact Profile (COHIP)
Tsakos et al. [28]	Scale of Oral Health Outcomes for 5-year-old children (SOHO-5)

of oral conditions on basic daily life activities [21, 22]. Its items refer to difficulty eating; difficulty speaking; difficulty cleaning teeth; difficulty relaxing (including sleeping); smiling, laughing and showing teeth without embarrassment; emotional problems (for example, being more easily upset than usual); difficulty carrying out major work or role; and problems enjoying contact with other people. By measuring also the severity of oral impacts, the OIDP assesses how important was the effect of oral impacts on the daily life of the person, rather than only how frequently they occurred. In addition, the OIDP provides also the option for a condition-specific score, whereby the reported oral impacts are attributed to a specific condition (e.g. dental caries or periodontal disease) by directly asking the respondent about the perceived cause of the oral impact. This allows a more precise link of the oral impacts to specific oral conditions and therefore makes it more suitable for assessing oral health needs.

The Geriatric/General Oral Health Assessment Index (GOHAI) consists of 12 items that are assumed to fall under three underlying constructs (physical function; psychological function; pain and discomfort) and aim to evaluate the frequency of problems and psychosocial impacts related to oral health in the past 3 months. The items are the following: eating without discomfort; limit foods due to oral problems; trouble in biting/chewing; trouble in speaking; uncomfortable eating with people; being nervous/self-conscious; limit social contacts; being worried/concerned; use medication for teeth; sensitive teeth or gums; being pleased with how your teeth look; being able to swallow comfortably. It was initially developed for elderly populations but was subsequently used also among adult populations in general.

All these three OHRQoL measures for adults have been adapted, validated and translated into a wide range of languages for use in many different settings and population and patient groups. A key attribute is that the questions for these measures were initially derived by lay people and patients rather than by health professionals alone. Furthermore, among the OHRQoL measures for adults, the OHIP and the OIDP have strong theoretical underpinnings as they are conceptually guided by Locker's oral health outcomes framework [7], though they have slightly different focus in terms of the aspects covered. In that respect, the OHIP attempts to address all constructs of the framework with the intention to provide a profile of all potential oral impacts, while the OIDP focuses on the constructs of disability and handicap. The GOHAI is based on a 'patient-centered definition of oral health' without further specifying its overall theoretical framework.

In essence, they all claim to measure the same construct, but their focus is not without variation, illustrating the conceptual multiplicity of the instruments. Most available OHRQoL measures report 'negative' impacts of disease on function, comfort and well-being. Some researchers have also advocated the measurement of 'positive' aspects of oral health [29], although reservations have been expressed concerning the interpretation of these measures and lack of consensus on the meaning of positive health [30]. The OHRQoL measures' content similarities relate to covering the broader themes of physical (physical health status and functioning), emotional/psychological and social well-being (social functioning). On the other hand, they demonstrate differences in their specific content/questions, precise aims and potential applications, as well as on their technical characteristics of measurement. These are characteristics worth considering when deciding which measure suits better a specific research question and study. On a strong conceptual critique of the main available OHRQoL measures, Locker and Allen [10] used criteria to assess whether they measure the underlying construct of 'oral health-related quality of life' and concluded that they 'do not unequivocally establish the meaning and significance of the impacts (of oral conditions)'.

Among the OHRQoL measures for child populations, the most widely used refer to the Child Perceptions Questionnaire (CPQ) [24], the Child-OIDP [25] and the Child Oral Health Impact Profile (COHIP) [27] among those providing self-reports of the children themselves in relation to how oral conditions affect their quality of life. Like for the measures for adults, the CPQ and the COHIP assess the frequency of oral impacts while the Child-OIDP assesses both the frequency and severity of oral impacts. In addition, the Early Childhood Oral Health Impact Scale (ECOHIS) has been widely used to provide parental proxy reports for the impact of oral conditions on the child's quality of life as well as cover aspects around the impact of the child's oral conditions on the life of the family [26]. Parental reports could be very helpful particularly for younger children when their developmental stage and limited experience of oral diseases may make self-reports challenging and of questionable validity. However, more recently valid and reliable OHRQoL measures based on self-reports have been developed for young children, such as the Scale of Oral Health Outcomes for 5-year-old children (SOHO-5) [28].

20.4 Measurement Properties and Key Characteristics

When deciding which measure to use, it is important to consider what it is you are trying to measure. The actual definition of 'Quality of life' [3] indicates its very broad range of constructs directly involved and/or playing a key role in it (► Box 20.2). Indeed, 'Quality of Life' is a

dynamic construct [31], with multiple influences, and it does not lend itself well to measurement.

Box 20.2 Definition of Quality of Life [3]

» …an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations and standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to the salient features of their environment.

There are many measures available, ranging from scales with fewer than 15 questions to multidimensional indices. Some authors have even advocated the use of a single global statement to measure 'quality of life'. Given the aforementioned complexity in measuring quality of life, it seems highly improbable that this can be captured using a single question. Locker and Quinonez [32] analysed data from Toronto and concordance between self-report global statements and the OHIP. They reported that there was significant discordance between these scores, indicating that they are measuring different attributes. Accordingly, measuring health-related quality of life requires a multi-dimensional scale. The main requirements and attributes of a health status measure are [33–35]:

1. Conceptual/measurement model, multi-dimensional construct. Measures rooted in theoretical models tend to have conceptual clarity, and this facilitates more appropriate measurement of the underlying constructs. In keeping with the socio-environmental model of health, a measure must assess many dimensions. These may include Physical function – e.g. mobility, self-care; Emotional function – e.g. depression, anxiety; Social function – e.g. intimacy, social contact; Role performance – e.g. work; Pain.
2. Reliability. This takes two main forms: (a) Internal Reliability (Homogeneity), which refers to the consistency of the different items within a measure, and (b) Test–retest reliability (reproducibility), i.e. produce the same results with repeated use under the same conditions.
3. Validity, i.e. how well we actually measure what we are trying to measure. There are many components to this, including face and content validity that assess whether the questionnaire covers all relevant content, construct validity (e.g. are we using a measure that is sensitive to oral health?) and discriminant validity. This is particularly relevant in descriptive population health studies or surveys, where ideally you can identify sub-groups of the population who have significant negative impacts of oral health on quality of life as a consequence of disease. Once validity properties have been demonstrated for assessment of specific conditions or populations, it cannot be assumed for a measure to be valid for all circumstances.
4. Appropriateness – refers to how relevant the measure is to the group being assessed. It is essential to think carefully about what is being assessed prior to using a health status measure.
5. Sensitivity/Responsiveness to change is an essential requirement of a health status measure in clinical trials and longitudinal studies. This property is also referred to as the 'responsiveness' of the measure. Ideally, a measure should be capable of detecting small changes over time. Fitzpatrick et al. [33] identified four factors that may hinder the responsiveness of a measure. First, the use of a generic measure with a large number of statements may include several items not relevant to the group in question. Second, the measure may contain too few quality of life domains and may not therefore be sensitive to subtle changes. Third, the instrument may contain items not readily affected by a clinical intervention, such as the pattern of social relationships. Finally, the measure may be subject to ceiling or floor effects, i.e. unable to register further improvement or deterioration in subjects (if a narrow range of responses are available).
6. Linked to this is the interpretability of the measure. While responsiveness refers to the ability to detect changes when they occur, interpretability addresses the question as to whether such changes/differences are meaningful or not. This is based on the minimally important difference (MID), which is the smallest score or change in score in the domain of interest that would be considered important from the patient's or clinician's perspective [36, 37]. Clearly, this facilitates interpretation of OHRQoL scores and is therefore a crucial feature for their application in clinical practice.
7. Practical utility – involves using a measure that only contains sufficient items to answer the research question. This is particularly relevant in clinical settings, as using a large generic questionnaire may not be feasible. Care is required with this approach, however, as shorter instruments may omit items which may be relevant to the population in question. There is, therefore, a trade-off between comprehensiveness and precision of the measure with practical utility. Shortened versions of measures, e.g. OHIP-14, have demonstrated good validity and sensitivity properties. Condition-specific versions of the OHIP, for example the OHIP-20 [38] have expanded the subset of items with a view to capturing items of importance to that condition and thus improving sensitivity to change in intervention studies. Using the

condition-specific version of the OIDP resulted in generally better performance of the OHRQoL measure in terms of sensitivity to change and also more precise calculation of the oral impacts for a specific oral condition, for patients with periodontitis for example [39].

An additional consideration is whether to use 'generic' or 'disease/condition-specific measures', or both. We have previously discussed this in relation to oral health, but there is a discussion to be made about the potential use of generic health measures to assess OHRQoL. These are general measures of health status having a number of important advantages. The psychometric properties of these measures are known, and comparisons can be made between populations with different problems using these scales. An example of a generic health status measure is the Short Form (SF) 36, or its shortened version SF12. However, these measures do not have good construct validity for oral health, and therefore, their use as an outcome measure for oral health is debatable. On the contrary, OHRQoL measures tap into oral health as a construct and are thus likely to capture the impacts of disease and its consequences on oral health-related quality of life.

Finally, when a measure is used in a different setting or culture from the one developed, it is essential to consider carefully its cultural and linguistic adaptation. This goes beyond a simple translation and relates to the measurement of a similar phenomenon in another culture through the use of an equivalent instrument. This process takes place before the validation of the measure in the 'new' culture/setting and should include a two-way (forward and backward) translation of the measure and the evaluation of its conceptual and functional equivalence.

20.5 How Have They Been Used? Applications

Since the early contributions to the relevant literature, quality of life (and later OHRQoL) measures were seen as the solution to many different problems, and this was reflected in their potential applications. Subjective measures of general health status and quality of life were initially considered relevant for (a) measuring the efficiency or effectiveness of medical interventions; (b) assessing the quality of care; (c) estimating the health needs of a population; (d) improving clinical decisions and (e) understanding the causes and consequences of differences in health [40]. In terms of subjective oral health outcomes, Locker [41] postulated a wide range of uses: (a) a political application that could be used to shape resource allocation; (b) a theoretical role in terms of shedding light on important relationships; and (c) more practical applications that cover research (clinical trials, health policy studies), public health (population-based surveys) and clinical practice (focus on individual).

However, a large volume of the relevant literature refers to cross-cultural adaptation and validation studies, i.e. adapting these measures for different settings and populations and demonstrating their adequate psychometric properties. In more recent years, these outcome measures have also been widely used in oral health research in the following contexts [42]:

- Epidemiological surveys demonstrating the impact of oral conditions on people's quality of life. Actually, they are nowadays increasingly incorporated in national epidemiological surveys.
- Studies exploring their potential use, in combination with clinical measures, in assessing needs for dental care.
- Clinical trials measuring the effectiveness of interventions, where OHRQoL measures are used as either primary or secondary outcomes, in addition to clinical assessments.

Much of the published research has reported from cross-sectional descriptive population studies, a number of which have been nationally representative health surveys. Data have been reported in terms of prevalence and severity of oral impacts. In general, the data confirm what might be suspected: oral health-related quality of life is negatively impacted by untreated dental decay and periodontal disease. This finding is closely associated with self-reported pain and functional limitation as a consequence of severe tooth loss. Indeed, there are now a number of systematic reviews synthesizing the available literature and demonstrating the impact of oral conditions, such as tooth loss [43] and periodontal disease [44], on OHRQoL, while the respective evidence for the impact of oral conditions on health-related quality of life is less conclusive with more mixed results [45].

Interestingly, some studies went beyond the description of oral impacts and engaged on analytical epidemiology and attempted to address more complex research questions. For example, Steele et al. [46] used national survey data from the United Kingdom and Australia to demonstrate that age and tooth loss had independent associations with oral health-related quality of life. Age was inversely correlated with OHRQoL, with reducing oral impacts in older ages. However, as tooth loss increased, so too did negative impacts on OHRQoL. There appeared to be a threshold with significant deterioration in OHRQoL once there were fewer than 20 remaining natural teeth, irrespective of having a denture to replace missing teeth. Differences between the Australian and UK data suggest that cultural and societal context may influence subjective oral health, and this has implications for planning of oral health services in an aging population. In a survey of Australian

adults, Slade and Sanders [47] reported that subjective oral health is better in older age than younger generations. The data suggest that older adults show a degree of resilience in adapting to the consequences of disease as they age.

Another avenue of relevant research relates to using OHRQoL measures in the process of testing whether relevant conceptual models have also empirical evidence to support them. Using structural equation modelling on data from a study of older adults in Canada, Baker, Gibson and Locker [48] questioned the conceptual basis of the OHIP and called for further conceptual development of the scale, and Locker's model. Similar analyses on a sample of patients with xerostomia supported Wilson and Cleary's conceptual model of patient outcomes [49].

Secondary data analyses of epidemiological studies have facilitated research on the existence and specific pattern of oral health inequalities in different countries, mostly showing social gradients in OHRQoL (e.g. [50, 51]). A study in Brazil has focused on socioeconomic life course effects and showed that childhood socioeconomic position had indirect effects on OHIP via adulthood socioeconomic position [52]. Using data on the OHIP-14 from two national surveys in the United Kingdom (Adult Dental Health Surveys 1998 and 2009), it was possible to evaluate and decompose changes in OHRQoL over time, thereby showing that the improvement in OHRQoL was mostly due to improvements in clinical oral health and the effect of ageing, with notable variations across the life course and age cohorts [53].

There is a relatively smaller volume of literature in terms of clinical trials and intervention studies, with the most widely reported area of study being the outcome of tooth replacement strategies using conventional and implant retained prostheses. These studies have largely shown that implant retained prostheses substantially improve the OHRQoL of edentate adults and help reduce the morbidity associated with total tooth loss [54]. This fits nicely with the concept that we do not 'cure' patients with tooth loss, but intervene to reduce morbidity. This can be achieved by a number of means, and conventional treatment may be as effective as implant retained restorations in improving oral health-related quality of life. In the case of edentate patients, the benefits are not uniformly spread across all. Many edentate adults have adapted to edentulism, and cope well with conventional replacement dentures. However, a significant number of edentate adults do not cope well with total tooth loss, and their quality of life is severely impacted and not improved with conventional dentures. Using an instrument with good discriminant validity, it is possible to identify such sub-groups within an edentate population and target them for implant-retained prostheses [55]. A recent systematic review looked at studies reporting the OHRQoL of patients with partial edentulism after different dental prosthetic treatments. The authors found some evidence, but overall it was a broadly unconvincing picture. There was some evidence that fixed prostheses based on implants performed adequately and slightly better than other prosthetic treatments [56].

Apart from the area of tooth replacement, there are many other studies on oral health using OHRQoL outcomes to evaluate oral health interventions to the level that there are also relevant systematic reviews synthesizing the evidence. For example, there is evidence that nonsurgical periodontal treatment resulted in improvement in OHRQoL, irrespectively of which instrument (i.e. lasers vs. traditional instrumentation) or technique of nonsurgical instrumentation was used [57]. And a systematic review on children undergoing general anaesthesia for the treatment of caries showed that it resulted in overall improvements in proxy-reported OHRQoL, though the heterogeneity of the relevant research limited the conclusions that could be drawn [58].

20.6 Issues in OHRQoL Research: (Mis) interpretation

A further issue is the reporting of studies which use OHRQoL instruments as outcome measures. Tradition has dictated the use of probability values of statistical significance. This can be misleading given that the 'values' of the scores derived by computing response codes are intrinsically meaningless in isolation. Accordingly, it is possible that within subject or between group comparisons reported as *P* values may show significant differences. However, these differences may not actually have had a meaningful clinical impact on the participants concerned. Consequently, a 'benefit' can be ascribed to an intervention, which is not real or inflated in its importance. Many authors have discussed this phenomenon in quality of life research and cautioned against reliance on statistical significance.

When evaluating the impact of a therapy, or when comparing treatment interventions, the treatment should at the very least reach the threshold of having an impact that the participant regards as meaningful. In quality of life research, the term 'minimally important difference' (MID) has been proposed to capture this intent. Jaeschke, Singer and Guyatt [59] defined MID as 'the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management'. It has been suggested that MID scores are reported in addition to probability values for intervention studies (within and between group comparisons) and also for noninterventions studies in terms of the differences between groups. As previously mentioned, the calculation of the MID is

Table 20.2 Minimum reporting standards for studies using OHRQoL outcomes [42]

	Cross-sectional	Longitudinal
Description		
Mean/median	×	×
Alternative scoring formats	×	(×)
Change scores distribution		×
Interpretation		
Statistical significance	(×)	(×)
Effect size	×	×
Standardised response mean		×
Standard error of measurement	×	×
Global ratings	×	×
Clinical benchmarks	×	×

essential in terms of answering the question whether the differences or changes observed are meaningful from the patient's or clinician's perspective [36, 37]. MID scores may also be used in cost effectiveness studies as means of comparing cost of treatments relative to the clinical impact of those treatments.

Tsakos et al. [42] commented on the issue in relation to OHRQoL measures and showed that different sets of responses end up with the same aggregate OHRQoL score, making it impossible to associate a certain score with a specific profile in terms of oral health and quality of life. They argued that 'reporting aggregate scores and assessing the statistical significance of differences is insufficient in and of itself' and advocated the routine use and reporting of the MID, as well as statistical significance, for both cross-sectional and longitudinal studies as a way of facilitating interpretation of otherwise meaningless OHRQoL scores (Table 20.2).

20.7 What Way Forward?

Even if we describe the available measures as patient-rated outcome measures or health status measures, they have provided a vehicle for patient/subjective input in evaluation of disease impact. And this is a considerable contribution on its own. We now have concrete evidence of the varying impact of oral disease on daily living on children and adults and no longer rely solely on clinical measures of disease to plan care.

Where we are still somewhat lacking is in linkage of this information to wider domains such as health utility and value-based health care. Health systems are under severe pressure to manage health costs associated with increasing prevalence of chronic disease and morbidity in ageing populations. As well as the obvious requirement to curtail cost, clinicians and administrators are increasingly asked to justify the cost of care provided and its value. Value-based health care and how to define this has become increasingly topical. In a number of health-care systems, 'value' is defined as the ratio of cost to patient outcomes ($V = C/O$). Measuring outcomes includes the use of patient ratings, such as patient-reported outcome measures or health-related quality of life measures, as well as objectively measured outcomes (e.g. complication rates). In the current economically stretched environment, the use of value-based outcomes may potentially strengthen the case for expensive interventions such as implant-retained prostheses. Cost of such care is expensive, but if substantial improvement in health-related quality of life is gained with minimal complications compared with less expensive alternatives, the value gain may be considered worthwhile. Further work is required to demonstrate the economic value of patient-reported health improvement, particularly on a population level.

Over the past two decades, at policy making level, there has been some success in incorporating subjective health status measures into large national surveys. This is an acknowledgement that subjective health status measurement is equal in importance to the traditional collection of clinical measures of disease. Clearly, we are now in an era where it is understood that we need both in order to fully capture the benefits of good oral health and impacts of disease on well-being. What is, arguably less clear-cut is whether such data have been used to drive health policy and service planning. A shift in research towards more analytical epidemiological studies including OHRQoL measures, their incorporation into methods of assessing oral healthcare needs and their use as outcomes in evaluating interventions and policies is well overdue.

Finally, as mentioned earlier in the chapter, many of the existing OHRQoL measures are based on an old conceptual framework, the ICIDH. We now need measures that are aligned with the ICF framework. This will require a substantial effort that may include development of new or adaptation of existing measures that would in any case need to be tested empirically and measure up conceptually. Data collected using measures aligned to the ICF framework can be used in planning future services and may be useful in advocacy for the benefits of a natural and functional dentition into old age.

Acknowledgement We thank Carolina Machuca Vargas for drafting the comprehensive list of oral health related quality of life measures (presented in the Appendix).

Appendix: Comprehensive List of Oral Health-Related Quality of Life Measures (Tables 20.3, 20.4, and 20.5)

Table 20.3 Generic oral health-related quality of life measures (developed for adults initially)

Instrument		Authors
Dental Health Questions from Rand Health Insurance Study	HIS	Brook et al. [60]
Geriatric/General Oral Health Assessment Index	GOHAI	Atchison and Dolan [23]
Oral Health Impact Profile	OHIP	Slade and Spencer [61]
DENTAL	DENTAL	Bush et al. [62]
Social Impacts of Dental Diseases	SIDS	Sheiham et al. [63], Slade [20]
Oral Impacts on Daily Performances	OIDP	Adulyanon and Sheiham [21], Tsakos et al. [22]
Dental Impact Profile	DIP	Strauss [64]
Dental Impact on Daily Living	DIDL	Leao and Sheiham [65]
Subjective Oral Health Status Indicators	SOHSI	Locker [66]
Oral Health Quality of Life inventory	OH-QOL	Cornell et al. [67]
Oral Health-Related Quality of Life for Dental Hygiene	OHRQOLDH	Gadbury-Amyot et al. [68]
United Kingdom Oral Health-Related Quality of Life Measure	OHQOL-UK	McGrath and Bedi [69]
Oral Health Impact Profile for Edentulous Adults	OHIP-EDENT	Allen and Locker [38]
Dental Health Status Quality of Life Questionnaire	DS-QoL	Brennan and Spencer [70]
Oral Health-Related Quality of Life Measure	OHRQOL	Kressin et al. [71]
Oral Health Impacts on Daily Living	OHIDL	Liu et al. [72]

Table 20.4 Condition specific oral health-related quality of life measures

Instrument		Authors
European Organisation for Research and Treatment of Cancer Head and Neck questionnaire	EORTC: HN	Bjordal et al. [73]
The Xerostomia Inventory	XI	Thomson et al. [74]
The Xerostomia- Related Quality of Life Questionnaire	XeQOLS	Henson et al. [75]
University of Washington Quality of Life Questionnaire	UWQOL	Rogers et al. [76]
The Orthognathic Quality of Life Questionnaire	OQLQ	Cunningham et al. [77]
The Liverpool Sicca Index	LSI	Field et al. [78]
The Liverpool Oral Rehabilitation Questionnaire	LORQ	Pace-Balzan et al. [79]
Manchester Orofacial Pain Disability	MPDS	Aggarwal et al. [80]
Psychosocial Impact of Dental Aesthetic Questionnaire	PIDAQ	Klages et al. [81]
Surgical Orthodontic Outcome Questionnaire	SOOQ	Locker et al. [82]
Oral Health Impact Profile for Dental Aesthetics	OHIP-aesthetics	Wong et al. [83]

(continued)

Table 20.4 (continued)

Instrument		Authors
Dentine Hypersensitivity Experience Questionnaire	DHEQ	Boiko et al. [84]
Prosthetic Quality of Life Questionnaire	PQL	Montero et al. [85]
Quality of Life with Implant-Prostheses	QoLIP-10	Preciado et al. [86]
Quality of Life associated with Dental Aesthetic Satisfaction	QoLDAS	Perea et al. [87]
Oral Potentially Malignant Disorders Quality of Life	OPMDQoL	Tadakamadla et al. [88]
Oral Health Impact Profile for Chronic Periodontitis	OHIP-CP	He et al. [89]
Oral Health Related Quality of Life-Oral Submucous Fibrosis	OHRQoL-OSF	Gondivkar et al. [90]
Chronic Oral Mucosal Diseases Questionnaire	COMDQ	Sansare et al. [91]

Table 20.5 Oral health-related quality of life measures (developed for children)

Instrument		Authors
Child Health Questionnaire	CHQ-PF50	Landgraf et al. [92]
Pediatric Quality of Life Inventory	PedsQL	Varni et al. [93]
The Dental Freetime Trade-Off scale	DFTO	Fyffe et al. [94]
Child Perception Questionnaire	CPQ	Jokovic et al. [96]
Family Impact Scale	FIS	Locker et al. [95]
Parental Perception Questionnaire	PPQ	Jokovic et al. [96]
Michigan Child Oral Health-Related Quality of Life Scale	MCOHQOL	Filstrup et al. [97]
Child Oral Impacts on Daily Performances	C-OIDP	Gherunpong et al. [25]
The Dental Discomfort Questionnaire	DDQ	Versloot et al. [98]
The Impact of Fixed Appliances Questionnaire	IFAQ	Mandall et al. [99]
Child Oral Health Impact Profile	COHIP	Broder et al. [27]
Early Childhood Oral Health Impact Scale	ECOHIS	Pahel et al. [26]
The Child Dental Pain Questionnaire	Child-DPQ	Barrêtto et al. [100]
The Oral Health-Related Quality of Life for Patients with Hypodontia	OHRQoL-Hypodontia	Akram et al. [101]
The Pediatric Oral Health-Related Quality of Life	POQL	Huntington et al. [102]
The Scale of Oral Health Outcomes for 5-year-old children	SOHO-5	Tsakos et al. [28]
The Oral Health-Related Early Childhood Quality of Life	OH-ECQOL	Mathur et al. [103]
Malocclusion Impact Questionnaire	MIQ	Patel et al. [104]
Child Oral Health Impact Profile - Preschool version	COHIP-PS	Ruff et al. [105]
Teen Oral Health-Related Quality of Life instrument	TOQOL	Wright et al. [106]

References

1. Kaplan RM. The significance of quality of life in health care. Qual Life Res. 2003;12 Suppl 1:3–16.
2. Guyatt GH, Feeney DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118:622–9.
3. The WHOQOL Group. The development of the World Health Organisation Quality of Life Assessment Instrument (the WHOQOL). In: Orley J, Kuyken W, editors. Quality of life assessment: international perspectives. Heidelberg: Springer; 1994.
4. European Court of Justice. Ruling on the case of Yvonne Watt's hip replacement. Luxembourg; 2006.
5. Cohen LK, Jago JD. Toward the formulation of sociodental indicators. Int J Health Serv. 1976;6:681–98.
6. Sheiham A, Croog SH. The psychosocial impact of dental diseases on individuals and communities. J Behav Med. 1981;4:257–72.
7. Locker D. Measuring oral health: a conceptual framework. Community Dent Health. 1988;5:3–18.
8. Reisine ST. The impact of dental conditions on social functioning and the quality of life. Annu Rev Public Health. 1988;9:1–19.
9. Gift HC, Atchison KA. Oral health, health, and health-related quality of life. Med Care. 1995;33(11 Suppl):NS57–77.
10. Locker D, Allen F. What do measures of 'oral health related quality of life' measure? Community Dent Oral Epidemiol. 2007;35:401–11.
11. Hunt SM. The problem of quality of life. Qual Life Res. 1997;6:205–12.
12. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. Health Technol Assess. 1998;2:i–iv, 1–74.
13. Locker D. An introduction to behavioural science and dentistry. London: Routledge; 1989.
14. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273:59–65.
15. Glick M, Williams DM, Kleinman DV, Vujicic M, Watt RG, Weyant RJ. A new definition for oral health developed by the FDI World Dental Federation opens the door to a universal definition of oral health. J Am Dent Assoc. 2016;147:915–7.
16. Ni Riordain R, Glick M, Al Mashhadani SSA, Aravamudhan K, Barrow J, Cole D, Crall JJ, Gallagher JE, Gibson J, Hegde S, Kaberry R, Kalenderian E, Karki A, Celeste RK, Listl S, Myers SN, Niederman R, Severin T, Smith MW, Thomson WM, Tsakos G, Vujicic M, Watt RG, Whittaker S, Williams DM. Developing a standard set of patient-centred outcomes for adult oral health – an international, cross-disciplinary consensus. International Dental Journal 2020 (early view).
17. Slade GD, editor. Measuring oral health and quality of life. Chapel Hill: University of North Carolina, Dental Ecology; 1997. www.adelaide.edu.au/arcpoh/downloads/publications/reports/miscellaneous/measuring-oral-health-and-qualityof-life.pdf.
18. Tsakos G, Allen PF, Steele JG. What has oral health related quality of life ever done for us? Community Dent Health. 2013;30:66–7.
19. Slade GD, Spencer AJ. Social impact of oral conditions among older adults. Aust Dent J. 1994;39:358–64.
20. Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol. 1997;25:284–90.
21. Adulyanon S, Sheiham A. Oral impacts on daily performances. In: Measuring oral health and quality of life. Chapel Hill: University of North Carolina; 1997. p. 151–60.
22. Tsakos G, Marcenes W, Sheiham A. Evaluation of a modified version of the index of Oral Impacts on Daily Performances (OIDP) in elderly populations in two European countries. Gerodontology. 2001;18:121–30.
23. Atchison KA, Dolan TA. Development of the geriatric oral health assessment index. J Dent Educ. 1990;54:680–7.
24. Jokovic A, Locker D, Stephens M, Kenny D, Thompson B, Guyatt G. Validity and reliability of a questionnaire for measuring child oral-health-related quality of life. J Dent Res. 2002;81:459–63.
25. Gherunpong S, Tsakos G, Sheiham A. Developing and evaluating an oral health-related quality of life index for children; the CHILD-OIDP. Community Dent Health. 2004;21:161–9.
26. Pahel BT, Rozier RG, Slade GD. Parental perceptions of children's oral health: the Early Childhood Oral Health Impact Scale (ECOHIS). Health Qual Life Outcomes. 2007;5:6.
27. Broder HL, McGrath C, Cisneros GJ. Questionnaire development: face validity and item impact testing of the Child Oral Health Impact Profile. Community Dent Oral Epidemiol. 2007;35(Suppl 1):8–19.
28. Tsakos G, Blair YI, Yusuf H, Wright W, Watt RG, Macpherson LM. Developing a new self-reported scale of oral health outcomes for 5-year-old children (SOHO-5). Health Qual Life Outcomes. 2012;10:62.
29. McGrath C, Bedi R. A national study of the importance of oral health to life quality to inform scales of oral health related quality of life. Qual Life Res. 2004;13:813–8.
30. Locker D, Gibson B. The concept of positive health: a review and commentary on its application in oral health research. Community Dent Oral Epidemiol. 2006;34:161–73.
31. Allison PJ, Locker D, Feine JS. Quality of life: a dynamic construct. Soc Sci Med. 1997;45:221–30.
32. Locker D, Quiñonez C. To what extent do oral disorders compromise the quality of life? Community Dent Oral Epidemiol. 2011;39:3–11.
33. Fitzpatrick R, Fletcher A, Gore D, Spiegelhalter D, Cox D. Quality of life measures in health care. I: application and issues in assessment. BMJ. 1992;305:1074–7.
34. Aaronson N, Alonso J, Burnam A, Lohr KN, Patrick DL, Perrin E, Stein RE. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res. 2002;11:193–205.
35. Allen PF. Assessment of oral health related quality of life. Health Qual Life Outcomes. 2003;1:40.
36. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. Mayo Clin Proc. 2002;77:371–83.
37. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008;61(2):102–9.
38. Allen F, Locker D. A modified short version of the oral health impact profile for assessing health-related quality of life in edentulous adults. Int J Prosthodont. 2002;15:446–50.
39. Tsakos G, Bernabé E, D'Aiuto F, Pikhart H, Tonetti M, Sheiham A, Donos N. Assessing the minimally important difference in the Oral Impact on Daily Performances index in patients treated for periodontitis. J Clin Periodontol. 2010;37(10):903–9.
40. Ware JE Jr, Brook RH, Davies AR, Lohr KN. Choosing measures of health status for individuals in general populations. Am J Public Health. 1981;71:620–5.
41. Locker D. Applications of self-reported assessments of oral health outcomes. J Dent Educ. 1996;60(6):494–500.

42. Tsakos G, Allen PF, Steele JG, Locker D. Interpreting oral health related quality of life data. Community Dent Oral Epidemiol. 2012;40:193–200.
43. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes. 2010;8:126.
44. Buset SL, Walter C, Friedmann A, Weiger R, Borgnakke WS, Zitzmann NU. Are periodontal diseases really silent? A systematic review of their effect on quality of life. J Clin Periodontol. 2016;43:333–44.
45. Haag DG, Peres KG, Balasubramanian M, Brennan DS. Oral conditions and health-related quality of life: a systematic review. J Dent Res. 2017;96:864–74.
46. Steele JG, Sanders AE, Slade GD, Allen PF, Lahti S, Nuttall N, Spencer AJ. How do age and tooth loss affect oral health impacts and quality of life? A study comparing two national samples. Community Dent Oral Epidemiol. 2004;32:107–14.
47. Slade GD, Sanders AE. The paradox of better subjective oral health in older age. J Dent Res. 2011;90:1279–85.
48. Baker SR, Gibson B, Locker D. Is the oral health impact profile measuring up? Investigating the scale's construct validity using structural equation modelling. Community Dent Oral Epidemiol. 2008;36:532–41.
49. Baker SR, Pankhurst CL, Robinson PG. Testing relationships between clinical and non-clinical variables in xerostomia: a structural equation model of oral health-related quality of life. Qual Life Res. 2007;16:297–308.
50. Astrøm AN, Ekback G, Ordell S, Unell L. Social inequality in oral health-related quality-of-life, OHRQoL, at early older age: evidence from a prospective cohort study. Acta Odontol Scand. 2011;69:334–42.
51. Guarnizo-Herreño CC, Watt RG, Fuller E, Steele JG, Shen J, Morris S, Wildman J, Tsakos G. Socioeconomic position and subjective oral health: findings for the adult population in England, Wales and Northern Ireland. BMC Public Health. 2014;14:827.
52. Vendrame É, Goulart MA, Hilgert JB, Hugo FN, Celeste RK. Decomposing early and adult life social position effects on oral health and chronic diseases in a cross-sectional study of Southern Brazil. Community Dent Oral Epidemiol. 2018;46:601–7.
53. Tsakos G, Guarnizo-Herreño CC, O'Connor R, Wildman J, Steele JG, Allen PF. Explaining time changes in oral health-related quality of life in England: a decomposition analysis. J Epidemiol Community Health. 2017;71:1203–9.
54. Awad MA, Rashid F, Thomason JM, Piovano A, Spielberg GP, Scilingo E, Mojon P, Müller F, Spielberg M, Heydecke G, Stoker G, Wismeijer D, Allen F, Feine JS. The effect of 2-implant overdentures on oral health related quality of life in a pragmatic international multicentre study. Clin Oral Implants Res. 2014;25:46–51.
55. Allen PF, McMillan AS. A longitudinal study of quality of life outcomes in older adults requesting implant prostheses and complete removable dentures. Clin Oral Implants Res. 2003;14:173–9.
56. Ali Z, Baker SR, Shahrbaf S, Martin N, Vettore MV. Oral health-related quality of life after prosthodontic treatment for patients with partial edentulism: a systematic review and meta-analysis. J Prosthet Dent. 2019;121:59–68.e3.r.
57. Shanbhag S, Dahiya M, Croucher R. The impact of periodontal therapy on oral health-related quality of life in adults: a systematic review. J Clin Periodontol. 2012;39:725–35.
58. Knapp R, Gilchrist F, Rodd HD, Marshman Z. Change in children's oral health-related quality of life following dental treatment under general anaesthesia for the management of dental caries: a systematic review. Int J Paediatr Dent. 2017;27:302–12.
59. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10:407–15.
60. Brook RH, Ware JE Jr, Davies-Avery A, Stewart AL, Donald CA, Rogers WH, Williams KN, Johnston SA. Overview of adult health measures fielded in Rand's health insurance study. Med Care. 1979;17:iii–x, 1-131.
61. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health. 1994;11:3–11.
62. Bush LA, Horenkamp N, Morley JE, Spiro A. D-E-N-T-A-L: a rapid self-administered screening instrument to promote referrals for further evaluation in older adults. J Am Geriatr Soc. 1996;44:979–81.
63. Sheiham A, Cushing A, Maizels J. The social impacts of dental disease. In: Measuring oral health and quality of life. Chapel Hill: University of North Carolina; 1997.
64. Strauss RP. The dental impact profile. In: Measuring oral health and quality of life. Chapel Hill: University of North Carolina; 1997.
65. Leao A, Sheiham A. The dental impact on daily living. In: Measuring oral health and quality of life. Chapel Hill: University of North Carolina; 1997.
66. Locker D. Subjective oral health status indicators. In: Measuring oral health and quality of life. Chapel Hill: University of North Carolina; 1997.
67. Cornell JE, Saunders MJ, Paunovich ED, Frisch MB. Oral health quality of life inventory (OH-QoL). In: Measuring oral health and quality of life. Chapel Hill: University of North Carolina; 1997.
68. Gadbury-Amyot CC, Williams KB, Krust-Bray K, Manne D, Collins P. Validity and reliability of the oral health-related quality of life instrument for dental hygiene. J Dent Hyg. 2000;73:126–34.
69. Mcgrath C, Bedi R. Population based norming of the UK oral health related quality of life measure (OHQoL-UK©). Br Dent J. 2002;193:521–4.
70. Brennan DS, Spencer AJ. Comparison of a generic and a specific measure of oral health related quality of life. Community Dent Health. 2005;22:11–8.
71. Kressin NR, Jones JA, Orner MB, Spiro A. A new brief measure of oral quality of life. Prev Chronic Dis. 2008;5:A43.
72. Liu J, Wong MCM, Lo ECM. Development of oral health impacts on daily living questionnaire items - a qualitative study. Chin J Dent Res. 2017;20:79–88.
73. Bjordal K, Ahlner-Elmqvist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, Kaasa S. Development of a European organization for Research and treatment of cancer (eortc) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncol. 1994;33:879–85.
74. Thomson WM, Chalmers JM, Spencer AJ, Williams SM. The Xerostomia Inventory: a multi-item approach to measuring dry mouth. Community Dent Health. 1999;16:12–7.
75. Henson BS, Inglehart MR, Eisbruch A, Ship JA. Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. Oral Oncol. 2001;37:84–93.
76. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA. The addition of mood and anxiety domains to the University of Washington quality of life scale. Head Neck. 2002;24:521–9.
77. Cunningham SJ, Garratt AM, Hunt NP. Development of a condition-specific quality of life measure for patients with dentofacial deformity: II. Validity and responsiveness testing. Community Dent Oral Epidemiol. 2002;30:81–90.
78. Field EA, Rostron JL, Longman LP, Bowman SJ, Lowe D, Rogers SN. The development and initial validation of the Liverpool sicca index to assess symptoms and dysfunction in patients with primary Sj??gren's syndrome. J Oral Pathol Med. 2003;32:154–62.

79. Pace-Balzan A, Cawood JI, Howell R, Lowe D, Rogers SN. The Liverpool oral rehabilitation questionnaire: a pilot study. J Oral Rehabil. 2004;31:609–17.
80. Aggarwal VR, Lunt M, Zakrzewska JM, Macfarlane GJ, Macfarlane TV. Development and validation of the Manchester orofacial pain disability scale. Community Dent Oral Epidemiol. 2005;33:141–9.
81. Klages U, Claus N, Wehrbein H, Zentner A. Development of a questionnaire for assessment of the psychosocial impact of dental aesthetics in young adults. Eur J Orthod. 2005;28:103–11.
82. Locker D, Berka E, Jokovic A, Tompson B. Does self-weighting of items enhance the performance of an oral health-related quality of life questionnaire? Community Dent Oral Epidemiol. 2007;35:35–43.
83. Wong AHH, Cheung CS, Mcgrath C. Developing a short form of Oral Health Impact Profile (OHIP) for dental aesthetics: OHIP-aesthetic. Community Dent Oral Epidemiol. 2007;35:64–72.
84. Boiko OV, Baker SR, Gibson BJ, Locker D, Sufi F, Barlow AP, Robinson PG. Construction and validation of the quality of life measure for dentine hypersensitivity (DHEQ). J Clin Periodontol. 2010;37:973–80.
85. Montero J, Bravo M, Lopez-Valverde A. Development of a specific indicator of the well-being of wearers of removable dentures. Community Dent Oral Epidemiol. 2011;39:515–24.
86. Preciado A, del Rio J, Lynch CD, Castillo-Oyague R. A new, short, specific questionnaire (QoLIP-10) for evaluating the oral health-related quality of life of implant-retained overdenture and hybrid prosthesis wearers. J Dent. 2013;41:753–63.
87. Perea C, Preciado A, Rio JD, Lynch CD, Celemin A, Castillo-Oyague R. Oral aesthetic-related quality of life of muco-supported prosthesis and implant-retained overdenture wearers assessed by a new, short, specific scale (QoLDAS-9). J Dent. 2015;43:1337–45.
88. Tadakamadla J, Kumar S, Lalloo R, Gandhi Babu DB, Johnson NW. Impact of oral potentially malignant disorders on quality of life. J Oral Pathol Med. 2017;47:60–5.
89. He S, Wang J, Wei S, Ji P. Development and validation of a condition-specific measure for chronic periodontitis: oral health impact profile for chronic periodontitis. J Clin Periodontol. 2017;44:591–600.
90. Gondivkar SM, Bhowate RR, Gadbail AR, Gaikwad RN, Gondivkar RS, Sarode SC, Sarode GS. Development and validation of oral health-related quality of life measure in oral submucous fibrosis. Oral Dis. 2018;24:1020–8.
91. Sansare K, Kapoor R, Karjodkar F. Validity of chronic oral mucosal diseases questionnaire in oral submucous fibrosis. Clin Oral Investig. 2019;23:873–7.
92. Landgraf JM, Maunsell E, Speechley KN, Bullinger M, Campbell S, Abetz L, Ware JE. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. Qual Life Res. 1998;7:33–445.
93. Varni JW, Seid M, Rode CA. The PedsQL™: measurement model for the pediatric quality of life inventory. Med Care. 1999;37:126–39.
94. Fyffe HE, Deery C, Nugent Z, Nuttall NM, Pitts NB. The reliability of two methods of utility assessment in dentistry. Community Dent Health. 1999;16:72–9.
95. Locker D, Jokovic A, Stephens M, Kenny D, Tompson B, Guyatt G. Family impact of child oral and oro-facial conditions. Community Dent Oral Epidemiol. 2002;30:438–48.
96. Jokovic A, Locker D, Stephens M, Kenny D, Tompson B, Guyatt G. Measuring parental perceptions of child oral health-related quality of life. J Public Health Dent. 2003;63:67–72.
97. Filstrup SL, Briskie D, Da Fonseca M, Lawrence L, Wandera A, Inglehart MR. Early childhood caries and quality of life: child and parent perspectives. Pediatr Dent. 2003;25:431–40.
98. Versloot J, Veerkamp JSJ, Hoogstraten J. Dental Discomfort Questionnaire: predicting toothache in preverbal children. Eur J Paediatr Dent. 2004;5:170–3.
99. Mandall NA, Vine S, Hulland R, Worthington HV. The impact of fixed orthodontic appliances on daily life. Community Dent Health. 2006;23:69–74.
100. Barrêtto ER, Paiva SM, Pordeus IA. Validation of a child dental pain questionnaire instrument for the self-reporting of toothache in children. Pediatr Dent. 2011;33:228–32.
101. Akram AJ, Jerreat AS, Woodford J, Sandy JR, Ireland AJ. Development of a condition-specific measure to assess quality of life in patients with hypodontia. Orthod Craniofac Res. 2011;14:160–7.
102. Huntington NL, Spetter D, Jones JA, Rich SE, Garcia RI, Spiro A III. Development and validation of a measure of pediatric oral health-related quality of life: the POQL. J Public Health Dent. 2011;71:185–93.
103. Mathur VP, Dhillon JK, Logani A, Agarwal R. Development and validation of oral health-related early childhood quality of life tool for North Indian preschool children. Indian J Dent Res. 2014;25:559.
104. Patel N, Hodges SJ, Hall M, Benson PE, Marshman Z, Cunningham SJ. Development of the Malocclusion Impact Questionnaire (MIQ) to measure the oral health-related quality of life of young people with malocclusion: part 1–qualitative inquiry. J Orthod. 2016;43:7–13.
105. Ruff RR, Sischo L, Chinn CH, Broder HL. Development and validation of the child oral health impact profile – Preschool version. Community Dent Health. 2017;34:176–82.
106. Wright WG, Spiro A, Jones JA, Rich SE, Garcia RI. Development of the teen oral health-related quality of life instrument. J Public Health Dent. 2017;77:115–24.

Further Reading

Fayers PM, Machin D, editors. Quality of life: the assessment, analysis and reporting of patient-reported outcomes. 3rd ed. Oxford: Wiley Blackwell; 2015.

Ecosocial Oral Health Epidemiology

Samuel Jorge Moysés and Ankur Singh

Contents

21.1 Introduction – 334

21.2 Historical Evolution of Modern Epidemiology – 335

21.3 Social or Critical Epidemiology – 336

21.4 From Social to Ecosocial: New Integrative Paths – 337

21.5 The Impact of Ecosocial Theory on Definitions of Causality in Epidemiology – 339

21.6 Applications in Oral Health Epidemiology – 340

21.7 Conclusion – 342

References – 343

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_21

Learning Objective

To apprehend new theoretical–methodological frontiers in oral health epidemiology, using solid theoretical frameworks that explore social determinants of oral health, the combination of quantitative and qualitative research methods and advanced analytical resources such as multilevel modelling.

21.1 Introduction

Science seeks permanent support in theoretical and methodological frameworks. Theory provides scientists with investigative rigor and hermeneutic depth in the interpretation of reality. Methodological frameworks support the capacity to test theories for confirmation, refutation or improvisation. Development of theoretical frameworks is guided by existing knowledge, diverse views, disciplinary boundaries and researchers' beliefs, often leading to disagreements. Such disagreements result in conflicts and sometimes generate unique opportunities to integrate strengths across disciplines [1, 2]. Like any other scientific branch, epidemiology also presents with diverse and often conflicting theoretical and methodological frameworks.

In epidemiology, the existing paradigms support the process of discovery, description and analysis of health-disease phenomena. Theoretical frameworks are pivotal to this discipline given they help in understanding of causal relationships and potential opportunities to break the causal chain to achieve goals for population health benefits. Such paradigms vary in their models of causal linkage, validation of hypotheses, search for associations or inferences that help explain and interpret the determinants of human illness or sustained health [3, 4]. Critically examining theories in epidemiology is fruitful as it provides scope for amplification of conceptual possibilities about causal determinants and refine existing theoretical explanatory perspectives.

At the same time, explanatory theoretical models define the way in which the health-disease process intervenes in a dynamic interaction with the fields of policy formulation, management decision-making, planning and evaluation, as well as the implementation of health practices [5–8]. Theories and applications of epidemiological knowledge go with the pace of scientific and technological development and are historically determined social practices. Important changes in, and incorporations of, the conceptual and instrumental repertoire have been observed in this area of human creation in recent decades [9, 10].

Before going further in developing the focus of the chapter, we must point out a critical note. It is possible to identify the recurring issue of opposing visions, an open conflict in the epidemiological field, in the specialized literature [11]. This perception has been earlier characterized by Poole and Rothman [12] as 'a war among competing visions of epidemiology'. This struggle expands to disputes beyond the academic world, reaching health systems/services, often misrepresented as a commotion arising from the practice of 'ideologization' of science. Perhaps one of the most notable poles of this problem, reflecting great political complexity and ideological dispute, can be identified in what has been termed 'critical Latin American epidemiology' [13–16]. This epidemiological school of thought has denounced and produced systematic criticisms of the other strand of epidemiology, the clinical epidemiology. The main criticisms are pointed to what they classify as hegemonic, positivistic-quantitative epidemiology and supposedly compromised by the interests and privileges of the rich nations of the northern hemisphere. Furthermore, such an approach does not pay due attention to key issues of social inequalities reflected in the health of vulnerable population groups in many nations.

This chapter is not focused on attempting to establish whether there has been, in fact, a 'war' between epidemiologists and their respective views and whether it persists today. For now, it suffices to recognize an unmistakable polyphony, that is, that there are several epidemiological accounts and strategies of knowledge adopted by practitioners of this vast scientific field. One of the most cogently disputed views is the level of analysis adopted to observe, experiment, record and analyse health-disease phenomena [17–19]. Susser [20, 21] classified this dispute into three strands, designating them by levels: *macrosocial, mesoindividual* and *micromolecular*. The first level corresponds to social epidemiology (socio-environmental or ecological), prioritizing the social determinants of the health-disease process. The second level corresponds to risk factors epidemiology, emphasizing individual behaviours and exposures. The third level is molecular (or genetic) epidemiology, focusing mainly on cellular biochemical mechanisms.

The epidemiological researchers, confronted with these three levels, could adopt different positions. For example, they could prioritize only one level, ignoring or minimizing the importance of the others; or they could seek an integration of two or more levels, recognizing the complexity of the phenomena and the importance of each level in the elucidation of parts of the whole. Certainly, besides the challenges inherent to the options adopted, it is noteworthy that they represent theoretical streams entering the epistemological debates of the philosophy of science [22–24]. Moreover, the choice of level of causal inquiry also places competing responsibilities of health to different parties. A micromolecular perspective places responsibility on health experts, such as doctors and dentists, a mesoindividual on individuals' abilities to manage their health, while a societal perspective stresses responsibility on policymakers.

One of the central debates in the health sciences is the dilemma between the theory of social determination of the health-disease process and the theory of the natural history of diseases, where the 'natural' is understood as the domain of the biomedical paradigm. This dilemma is visible throughout the history of the development of modern epidemiology, being evident in the changes of its concepts and most applied practices in each social context and historical period. The problem can, therefore, be addressed by the reconstitution of the development of epidemiology as a science, from its dominant paradigms and its observable consequences on the knowledge of the area [15, 20, 21, 25–42].

21.2 Historical Evolution of Modern Epidemiology

The causality of socio-environmental factors in multiple manifestations of morbidity and mortality has long been recognized. In the mid-nineteenth century, the dominant paradigm for explaining the health-disease process in populations was the 'miasma theory' [43, 44]. Harmful pestilences emanating from contaminated soil, stagnant water and putrefying matter were the causes of various diseases. This theory gained momentum in England when William Farr strengthened, from 1839, the old foundations of epidemiology that had been proposed by John Graunt in 1662, using specific diagnostic classifications for mortality statistics [45]. Farr broadened the use of vital event registration for health research since, up until then, this register was only directed to global mortality [46–50]. Although misguided in its model of disease causality, the miasma theory allowed the proposition of a socio-environmental perspective for health intervention, especially with the studies by Chadwick and Engels [16, 51]. These studies, following Rudolf Virchow famously statement that 'medicine is a social science, and politics nothing but medicine at a larger scale', contributed to establishing the belief that the main sanitation problems were of structural rather than individual origin and that their solution required comprehensive social interventions. It led to formulation of the Great Britain's first Public Health Act.

Unchanged for several decades, the miasma paradigm was progressively replaced by the advent of microbiology and parasitology; accordingly, the socio-environmental perspective was also gradually abandoned. Jakob Henle, John Snow, Louis Pasteur and Robert Koch emerged as emblematic figures, symbolizing the foundation of a new era for the study of the causal mechanisms of disease under the 'germ' or pathogen paradigm discovered by microbiology. In the meantime, the monocausal paradigm of infectious–contagious diseases already coexisted with precursors of the multifactorial view of epidemiology, such as Max von Pettenkofer [52–54]. Since its origin, the microbiological theoretical framework had implied a promising public health perspective, but what followed historically was a narrow development, dominated by a univocal causality model, based on the laboratory activity of searching for the specific etiological agents of each disease. One of the political implications of understanding causality from a narrow microbial perspective is that the locus of control was placed on individuals rather than on systems. When it was believed that the most important infectious agents of communicable diseases had been discovered, the strength of this paradigm also weakened. With notable exceptions, such as Rene Dubos [55], few had predicted the possibility of a new outbreak of communicable diseases or the emergence of new global epidemics, which in fact occurred later.

In the twentieth century, the physical and social environment was once again considered as an explanatory possibility in causal models after the recognition of the epidemiological importance of chronic-degenerative diseases, whose multiple causes were often complex and unknown. The epidemiology of chronic diseases was developed by Richard Doll, Austin Bradford Hill, Jeremy Morris, Thomas McKeown and others, whose studies were interpreted by Susser [21] as being inspired by the 'black box' paradigm. This metaphorical expression designates a self-sufficient unit of correlation between risk factors and health outcomes, whose internal biological/metabolic mechanisms are not naturally elucidated.

During the 1950s and 1960s, the study of the health-disease process in human groups intensified by following the logic of searching for multifactor models, implemented by the epidemiology of chronic diseases. Thus, models such as the Natural History of Diseases were proposed, integrating 'hosts', 'etiologic agents' and 'environment' to explain disease distribution. This triad of factors constitutes the classic paradigm of the twentieth century [56], which was rapidly disseminated in the health sciences. During the second half of that century, epidemiology was driven on the understanding of multiple disease causality processes [28]. The methodological accuracy and analysis techniques led to an uninterrupted refinement cycle. Epidemiologists have begun to explore the subtleties of confounding variables, erroneous data classification, validity and reproducibility, and related issues, which form the basis to newly operationalized causal thinking. Since initial studies began to be conducted under this paradigm, variations and gradients in the distribution of diseases have been correlated to factors such as family income, schooling, ethnic group, geographical location and economic activity.

While the epidemiology of chronic diseases gave rise to increasing complexities, involving the necessity

of more sophisticated study designs, with more robust statistical analysis techniques and multicausal inference models, the same cannot be said for theoretical development [28]. The metaphor of a 'causal network' characterizing the intricate nature of collective health problems, particularly of chronic diseases, was originally proposed in 1960 by MacMahon and Trichopoulos [57]. This framework has been widely spread and is still largely used. However, Krieger [58] considers it a poorly developed theoretical model, which reflects the priority given to the development of epidemiological methods, without the same effort being put forth in proposing consistent epidemiological theories. Relatively little work has been devoted to the development of concepts and models of the so-called epidemiological theory. The suggestive image of the 'web' of causation raises the question: who or what is the 'spider' that made it? [25, 36]

Krieger and Zierler [32] proposed the scathing metaphor of a 'spider-free web' to underline the lack of discussion about the theoretical assumptions that shape the network of disease causation. For them, the authors who proposed and formulated the application of this paradigm had never answered the question of what led to the construction of a 'spider-free web'. However, a more detailed inspection of the elements of the web would reveal the 'threads' of the subliminal theoretical orientation; the threads that are hidden when the fabric is braided in the loom. The web employed a kind of theoretical weighting that levels all determinations, in a scientific claim of 'neutrality' as to the interpretation of risk factors and their respective hierarchies. For instance, variables assessing 'access to clinical treatment', on the one hand and, on the other hand, 'socioeconomic condition' occupied the same hierarchical level and received the same weight.

The web inevitably drew attention to risk factors closer to health outcomes, later called 'proximal', as opposed to 'distal' factors [23, 24]. Proximal factors would represent the biological causes directly related to the disease, focusing on lifestyles, individual behaviours and other conditions that supposedly could be the object of medical intervention or individual resolution through resources such as information and personal education [59]. The web did not distinguish between the medial and distal determinants of disease in individuals and populations. It did not disentangle what Rose [60–62] called the differences between 'causes of cases' and the 'causes of incidence in the population'. These two configurations of causal determination are not necessarily the same, and their unfolding requires different questions and research methodologies [63].

For example, the question of why some individuals have excessive tooth cavities does not equate to the question of the over-prevalence of this condition in some disadvantaged populations. The first issue emphasizes individual susceptibility and interventions targeting 'high-risk individuals'; the second highlights the determinants that act on the population and interventions aimed at changing the distribution curve of the disease in the population, targeting at a better overall oral health condition [63–65].

These aspects of the 'web' allow the identification of biomedical individualism, often called the 'biomedical model', with its underlying theoretical framework. This model (i) emphasizes biological variables of the disease, subject to intervention by the health professional; (ii) considers the social determinants of the health-disease process as distal conditions, difficult to be operationalized in research, vague in their definitions (sometimes seen as 'confounding'), and therefore secondary if not irrelevant for intervention; (iii) perceives the population as a sum of individuals and addresses disease patterns in populations as a simple aggregate of individual cases [58, 66].

In the biomedical model, even when the term 'ecological study' is mentioned to characterize a type of design with aggregate units and population focus, it is understood as a 'naturalized' socio-environmental approach. This approach considers groups as an assembly of undifferentiated individuals, supposedly sharing similar conditions of life [13, 17, 21, 67–76]. When debating future paths for epidemiology, Susser [77] suggests that the focus of risk factors at the individual level – the hallmark of the biomedical model – would no longer be of much use in the future. In consequence, attention would be directed to causal models at the societal level, along with the models that address pathogenesis and causality at the molecular level.

21.3 Social or Critical Epidemiology

In the mid-nineteenth century, Rudolf Virchow proposed the understanding of epidemic diseases as a manifestation of social and cultural maladjustment. His proposal fit the social medicine movement, which was abandoned with the development of the positivist current of medicine, in which the biologist and individual approach prevailed [78].

Decades later, medicine and other areas of health once again incorporated environmental and societal issues into their models of causality. Besides the etiological and host agents, the environment started being considered an element of a mechanical equilibrium relationship. The mechanistic character of this conception can be evidenced in Gordon's proposition [79], which uses a scale to refer to the health-disease process. In one of the dishes of the scale, there was the agent with its capacity of aggression; in the other, the host with its ability to defend itself. The fulcrum of the scale was

represented by the environment. When in balance, these three elements represented health; the imbalance represented the disease. Subsequently, Ryle [80] and Leavell and Clark [56] used this triad to advocate a multicausal model of the natural history of diseases. This model, however, did not address inequality (or inequity) in the distribution of diseases among the different social groups and the factors that explain this difference.

The affirmation of the social character of the health-disease process extended from studies on the distribution of diseases and health conditions in different population groups and the conceptual discussion about the historical and social determinants of the disease, especially in the strata of urban workers and poor rural populations. The analysis of the health-disease process in the social context reinforced the conviction that health damages were not only biological but influenced by the way in which groups are embedded in the wider social processes and by the way political power is appropriate by the elites. It was necessary to go beyond the direct object of clinical medicine and classical epidemiology itself and to recognize the object of study not only in the individual but in the community and its struggles for survival and better living and health conditions [81–85].

Although clinical medicine often confines the individual to its biological nature – as an intervention strategy – critical epidemiology can focus on a broader dimension, identifying social processes that interfere with disease risk, such as living environment, work conditions or access to health services. By integrating the social dimension in health studies, the dearth of previously formulated causal disease models was demonstrated [86]. The unicausal model, which emphasized the etiological contribution of microbial agents, and the multicausal model applied to chronic-degenerative diseases were not enough to explain the health-disease complexity. To address this difficulty, Laurell [82] sought to articulate the health-disease process and the societal process, even recognizing the subordination of the first to the second.

Following Laurell's analytical guideline, several authors have proposed an appraisal of conventional models of epidemiology, criticizing them as analytical tools in the service of global capitalism and the lucrative medical-industrial complex. For these authors, the emphasis of the health-disease process to its biological aspects and drug-centred interventions conceals its social determination, subtracting the possibility of transforming the conditions of exploitation of labour in the realm of capitalism. In contrast to conventional epidemiology, several contributions in various national contexts advocated a 'new' epidemiology in the service of political and socioeconomic changes geared to the recognition of 'causes of causes', or social determinants of health, and the real needs of the most vulnerable social classes [87–96]. In this way, the conceptual bases of modern social epidemiology are invigorated, evidencing a strong scientific policy activism and clashes between its passionate defenders and its sharp critics [13, 19, 40, 45, 97–106].

21.4 From Social to Ecosocial: New Integrative Paths

The social epidemiologists have criticized the epidemiology of individual risk factors, designated by the 'black box' metaphor. They pointed out that this trend takes a shortcut and works with an individualized biomedical and statistical deviation regarding the true complexity of social determinants and the context of human groups. This leads to ignorance of important factors in avoidable diseases and early deaths, as well as of those promoting health. Concentration on the biological and behavioural aspects of individuals also neglects the preponderant influence of families, social groups, circles of relationships and community [21, 107–112]. The proponents of the epidemiology of risk factors and researchers sympathetic to this approach do not agree with this perception and present their arguments in favour of this approach [105, 106]. This reasoning seems to be useless to its opponents, for whom the dominant theoretical development of risk-factor epidemiology would ignore the true dialectic that involves the possibility of people realizing their full life potential and being healthy.

Susser [20, 21] identified impulses for a new era of epidemiological studies. Two dominant forces of our time, much explored in modern literature, begin to obscure the paradigm of the black box: a change in international health configurations (demographic and epidemiological transitions) and new technologies.

Concerning international health-disease patterns, no epidemiological event had more impact than the human immunodeficiency virus (HIV) and the corresponding epidemic. The epidemiology of risk factors is poorly equipped to wield epidemic control in this case. Data analysis at the individual level, as was done by the black box paradigm, does not allow us to consider, in a gradient of causality levels (exposure-outcome), the likely points with potential for greater success for interventions. In the case of HIV infection, immediate or 'proximal' causes and risk factors were known; however, this knowledge could not be translated into the protection of public health. Likewise, confidence in our ability to modify behaviours and control a disease that lead to increased mortality has been shaken. In retrospect, the belief in the control and overcoming of communicable diseases now seems naive and insufficient even for developed countries.

As to technology, the developments that may guide epidemiological research to a new paradigm lie mainly in genomics, proteomics and metabolomics; in biomaterials and biomedical techniques; and in big data information systems, including artificial intelligence, machine learning and algorithms for their explanatory and predictive tasks in the face of global epidemiological challenges. Advances in these areas begin to reform all disciplines in the health field. The technology involved in global network communication and information systems has opened new possibilities not only for capturing and manipulating mass behaviour (an unwanted outcome) but positively for understanding and preventing disease and promoting health.

In response to these new driving forces of epidemiology, multilevel quantitative approaches are presented, especially in the study of chronic non-communicable diseases [63]. They reveal an epistemological attachment with clear evocations of classical social epidemiology in the social–environmental question, but with different methodological approaches, particularly in the use of sophisticated, technology-intensive, quali-quantitative methods [24]. At the edge of this drive is a movement that advocates approaches that are based on critical and historical theory, advancing into issues such as social production/reproduction, disproportionate mechanisms and accumulations of risks for certain groups, and 'differential modes of life and health' [109, 111]. Through simultaneous examinations of societal and individual determinants of individual variations in health, along with share of individual variation in health outcomes that exist at the population level, multilevel approaches generate possibilities to move beyond one level of causation.

Nowadays, the theories used by epidemiologists linked to the renewed critical tradition gain varying (but convergent) taxonomies: (i) psychosocial theory; (ii) the social determinants of health theory; (iii) the political economy of health; (iv) the life-course theory, or theory of adverse conditions in early life cycles and their cumulative effects; (v) the ecosocial theory with multilevel approaches; and (vi) intersectionality theory. All seek to elucidate the intricacies for explaining social inequities in health and, at the same time, they embody theories of distribution of diseases that cannot be reduced to mechanisms of individual causality [110]. They differ substantially from previous theories on how they integrate social and biological aspects into explanation of the health-disease process and their respective directions for action [24, 25].

A socioecological paradigm for epidemiology implies that an exclusive focus on risk factors measured at the individual level will not meet the new socio-environmental and health system challenges. It will also be necessary to study the risk factors and their determinants measured at the social and environmental level, in parallel with the study of pathogenesis at the molecular level. A metaphor can illuminate this socio-ecological perspective: Susser [21, 53] compares this perspective to 'Chinese boxes' — a set of nested boxes, each containing smaller boxes. To Krieger [36], as an alternative metaphor, the closest image is that of a 'fractal', translating the interweaving of mutually mirroring levels, generating understanding from the subcellular to the societal level, echoing itself indefinitely. At each level, defined structures such as nations, social groups or communities can be regarded as unique and tangible relationships. At any level of the hierarchy, these relations are generalizable to the extent that they are well matched with structures associated with the other levels of analysis.

Contemporary changes that occur on a global scale inspire the new socioecological approaches. For example, the idea that the Holocene is over and a new man-dominated geological time, the Anthropocene is in progress, with human 'footprints' being progressively left on the planet. Climate change is seen as the main global environmental threat to health, but also recognizing other impacts, including the dramatic loss of tropical forests, land degradation, decrease of biodiversity, decline of freshwater resources and acidification of the oceans, with great population displacements by wars and natural disasters, among others [113]. Faced with such a historical transformation, there is a rebuff of ecosocial epidemiologists to adhere to a single analytical plane, since they endorse multilevel interpretive and operational milestones. Unlike previous representative diagrams, whether they are scales, or triangles connecting 'host', 'agent' and 'environment', or causal networks, the new illustrative representations are multidimensional and dynamic [23, 114].

Three of the new and main representations are the ecosocial framework, the eco-epidemiology schema and the socioecological systemic perspective. The ambition of these representations is not to offer an all-purpose theoretical–methodological agenda. Their target is to offer a set of integrative principles that can be gauged and can be useful for formulating investigative hypotheses and interventions directed at each level of analysis, with resonances that spread to cells, organs, individuals, families, communities, populations, societies or ecosystems [67]. As opposed to the biomedical model, the emergent socioecological paradigm in epidemiology is defended by some exponents of global health thinking and encompasses many levels of organization: molecular, individual and societal [111].

21.5 The Impact of Ecosocial Theory on Definitions of Causality in Epidemiology

Whatever the dominant paradigm, at any given time, an ever-present and relevant problem forces interim response on health practices: 'Why has this population developed this disease at this time?' A good clinical practice involves going beyond the questions 'what is the diagnosis?' or 'what is the treatment?' and also focus on 'why has this happened?' and 'could this have been prevented?' for this or that individual. Going even further, it would be necessary to focus on the determinants of population health, in line with the question posed by Evans, Barer and Marmor [112]: 'Why are some population groups healthy while others are not?' Rationale behind studying population variations in oral health and its societal determinants are also discussed recently in a review article [63].

Epidemiology is often defined as the study of the determinants of disease distribution [115]; then again, we should not forget that the more widespread a particular cause, the less it explains the distribution of cases. The most difficult cause to identify is the one that is universally present, because it will be difficult to detect any variation and thus the influence of this cause on the distribution of disease [60]. For a pragmatic epidemiology, in which all the determinants refer to causal hypotheses, the essential properties continue to be guaranteed by the Hill and Hill principles [116], concerning consistency, strength and specificity of causal associations, temporal sequence, predictive performance, and coherence or plausibility of the hypotheses. In this perspective, cause is something that makes a difference. Thus, epidemiology seeks the causes of health situations, looking for them in a 'proximal' dimension (etiological agents, biological, chemical, physical factors) and a 'distal' dimension (attributes of people, places, historical contexts) [117, 118].

Two apparently new observations have become prevalent in the ecosocial epidemiological literature. The first is that there is a socioeconomic gradient in health, extending across the entire social scale and not only as a poverty cut-off, separating those suffering extreme conditions from those who enjoy good health. The second is that area and context of life are of great importance, since people living in impoverished areas tend to have worse health conditions than those from better-off areas [25, 26, 89]. Income indicators are associated with health in three ways: by measuring the gross domestic product of countries, states, or cities; values of income earned by individuals; and measures of inequalities in the distribution of income among people living in the same geographic area.

However, there are important arguments in these new interpretations. A systematic critical review paper [119] examined 98 aggregate and multilevel data studies, in which associations between health and income inequality were estimated. The authors found little support for the idea that income inequality is a generalizable determinant of population-based health differences within rich or among rich countries, although income inequality could directly influence certain health outcomes, such as homicide in some contexts. Even if the authors have little support for a direct effect of income inequality on health per se, they concluded that reducing income inequality could help reduce health inequalities by improving the health of the whole population. Despite growing support for income inequality and health relationship recently [120], based primarily on the volume of supportive studies, the relationship still remains contentious [121].

A fundamental question concerns the degree to which these associations reflect etiological causality because, in this case, the redistribution of income should directly improve human health. According to Marmot [122], there are two ways in which income could be related to health regarding causality: by a direct effect on the material conditions necessary for biological survival and by an effect on the opportunities for social participation and conditions to control life circumstances.

The analytical orientation that seeks to develop the theory of ecosocial epidemiology emphasizes that past and present patterns of population health and disease are mainly due to social organization, and especially to its political and economic activities that generate health inequities [16]. This perspective is fundamentally different from another, which sees such patterns simply as the sum of individual characteristics and choices. According to the ecosocial view, social inequities in health constitute the defining problem of the discipline of epidemiology [66]. An ecosocial approach requires situating the social context that generates health behaviours so that people will be understood in their broader circumstances. Concerning prevention, research should be encouraged not only on proximal factors judged to be amenable to intervention by the health system, or the effort of individuals, but also on far-reaching determinants of health that can only be changed by wider social action [25, 26].

Furthermore, an ecosocial approach would challenge the stringent distinction between analysis at the individual and group levels [123]. As health care is a collective phenomenon that cannot be reduced to merely individual attributes, two fallacies should be avoided. The 'individualistic fallacy' assumes that individual data are sufficient to explain group phenomena. The 'ecological fallacy', in turn, results from the confusion in the process of grouping data, where spurious interpretation

of results based on averages and aggregate data does not necessarily reflect the concrete experience lived by individuals [17, 124]. The correction for both types of fallacy is the so-called contextual analysis, or multilevel analysis, which, among other characteristics, combines individual and group data in a clearly specified and theoretically justified manner using appropriate analytical techniques.

Clarifying the analytical unit of interest is also key to avoiding fallacies. A recent operationalization of new causal thinking grounded within the Potential Outcome Approaches framework [125] enables the quantification of separate contribution of contexts, and the distribution of individual characteristics within contexts, in population differences in health outcomes [126]. Nevertheless, gaps in application of causal modelling approaches in multilevel context persist [127]. Multilevel models further build the platform to study population variations in health outcomes with individual-level data, by studying the population-level share of individual variations in health using measures such as intraclass correlation coefficients, variance partition coefficients and median odds ratio.

Finally, it is worth remembering the problems of power and control that are frequently omitted from epidemiological literature. The advocates of a libertarian paradigm, open to dialogue and at the service of human health, would certainly benefit from the emergence of a 'political epidemiology' [128]. This epidemiology would conduct scientific study of political factors, social processes and subjective conditions underlying human motivations influencing the distribution of health-disease in different populations.

21.6 Applications in Oral Health Epidemiology

Even after decades of development of the so-called Public Health Dentistry, oral epidemiology moves between a single-sided, microbiological view, and a multifactorial view, with an emphasis on diet, hygiene habits and access to preventive measures such as fluoride [129]. Sometimes subjected to the hegemony of clinical-etiological models, oral epidemiology seems to reduce all causal analysis of its main worked condition, dental caries, to only one factor: cariogenic (acidogenic) microorganisms. Throughout its most productive time in the first half of the twentieth century, stimulated by classical studies on caries and fluoride [130], research patterns were still predominantly descriptive and remained as such for decades, with monotonous surveys on disease prevalence in the World Health Organization's age range indexes. Only recently has there been a new stimulus to epidemiological production in the area, with socially deeper and more creative approaches, from certain centres in Europe, North America, Latin America, Australia and New Zealand.

Providing an argument for this finding, Newton and Bower [131] acknowledge that research in oral epidemiology, at least until recently, has not advanced in the social determinants of oral health. This fact would be due to the limitation imposed by the absence of theoretical models that can reflect the real processes of social life, as well as the causal networks that interconnect the social structure with the oral health-disease process. With such dearth, traditional epidemiological research on oral health hardly addresses social determinants, as if they were isolated 'risk factors', attributable to the individual, with a minimal appreciation of how these factors interrelate in time and place and, being part of social life, how they influence oral health. Newton and Bower [131] still point to new theoretical–methodological frontiers to be explored, using solid theoretical frameworks that explore the social determination of diseases, the combination of quantitative and qualitative research methods and advanced analytical resources such as multilevel modelling.

On the other hand, as novelty and changes always come, a promising new research agenda in epidemiology and oral health services has recently been emphasized [132, 133]. Singh et al. [134] stress on the need for integration of social–epidemiological theories in studies of social inequality and oral health. Some examples from the literature will be highlighted. These studies focus on the search for theoretical support in explanatory models guided by the social determinants of (oral) diseases, as well as the use of multivariate analytical resources in hybrid designs that incorporate the multilevel structure of the analysis units.

▶ Examples

Pattussi et al. [135] conducted an ecological study to investigate possible associations of the dental-cavity profile of schoolchildren with the characteristics of their areas of residence, defined by gradients of social deprivation, income inequality and social cohesion. They concluded that the Gini coefficient, a strong indicator for social inequalities, was associated in a significant way with the inequalities found in the distribution of cavities.

Antunes et al. [136] innovate when assessing gender differences in the distribution of dental cavities and restorative treatments at the aggregate level, taking 'cities' as an ecological level of analysis. The study of 131 cities in the state of São Paulo, Brazil, indicates that 11- and 12-year-old female subjects had higher cavity incidence and greater use of dental services. The authors noted discrepant incorporation of dental services in cities where the socioeconomic profile of the population was poorer. ◀

Social determinants, as a special focus on the impact of healthy environments on oral health, were also explored by Moysés et al. [137]. These authors conducted a study with students with low family income enrolled in peripheral schools of Curitiba and beneficiaries of health promotion policies. Their objective was to evaluate whether their oral health was better than those of other schoolchildren with the same socio-spatial condition but enrolled in lower ranked schools. The total sample included 1823 schoolchildren in 33 public schools, and an index was created to classify schools based on their physical, environmental, curricular and social attributes, among other aspects. The best schools, called 'supportive', showed a profile of students' oral health superior to the profile of 'non-supportive' schools, both in the percentage of schoolchildren free of cavities and the prevalence of dental trauma.

Peres et al. [138] conducted an ecological study to investigate the association between socioeconomic indicators in 293 cities in Santa Catarina, Brazil, and the presence or absence of water fluoridation, as well as the year in which this measure was implemented. The results indicate that cities with larger populations with better child development rates and lower illiteracy rates are associated with a longer implementation time of water fluoridation.

Peres et al. [139] investigated the relationship of biological and social conditions experienced by 6-year-old children since an early age in their lives with the prevalence of dental cavities. Using data from a cohort study of 5249 live births, started in Pelotas, Brazil, in 1993, the authors were able to evaluate a sample of 400 children selected from this cohort, in 1999. They concluded that social and biological risk factors accumulated in early stages of life resulted in higher levels of dental cavities. Some of these factors are low parental schooling at the time of childbirth, height deficits at 12 months, children not attending child care centres at age six, as well as children with inadequate hygienic habits or high levels of sugar consumption.

Based on these few mentioned studies, which may be considered precursors of an oral health epidemiology with a more critical density and multilevel modelling, a growing number of publications has been adopting this approach [63, 121, 134, 140–148]. It seems clear from the examples presented here that new investigative possibilities are presented for oral epidemiology, with a predictable impact on the type and quality of evidence produced. This has renewed and expanded the frameworks of knowledge, with prospects for positively influencing the formulation of policies and organization of services aimed at the oral health of the population. Again, one trend that can most influence new approaches in oral epidemiology is the progressive use of ecosocial studies in multilevel designs. They adopt a typology called aggregate-observational-longitudinal, making an analogy to individual-based longitudinal studies. Thus, they allow the realization of the following:

1. Trend or time-series studies in which the same area or population is investigated at different times, or with hybrid architecture, in which several areas or populations are studied at different times to identify inequalities in the rate of reduction of monitored indicators.
2. Case–control studies of aggregate data, sometimes referred to as 'natural experiments', to observe a phenomenon or population process that is potentially pathogenic or life improving and that affects certain groups (experimental) but not others (control). Only when there was intervention controlled by the investigator would it be a true experiment involving aggregates rather than individuals and, in that sense, they would be called aggregated intervention data studies or, more commonly, community trials. The term 'natural experiment' is not correct in cases where the change of conditions did not follow some previous planning. These are observational studies (post-factum research), there being no control of the independent variable by intervention, nor randomness in the composition of the respective groups.
3. Cohort studies of clusters, which may include two types, depending on the nature of the aggregate taken as the reference base for the study. The first is territorially based research (census tracts, communities, neighbourhoods, districts, municipalities, states, nations, continents). The second are studies of institutional clusters (factories, schools, prisons and health units).

In the specific field of epidemiology, ecological designs have undergone an intense process of criticism and devaluation over the years, being relegated to the condition of purely descriptive approaches, without greater analytical power [149, 150]. From the 1990s, the logic and methodological bases of this type of study have been re-evaluated and valued even in the most traditional epidemiological means [151].

With the recognition of the importance of contextual factors and the development of analysis techniques in multilevel and structural equations, ecological studies are now possible, counting on dynamic designs suitable for research of health inequalities and technological evaluation of general and oral public health policies. The perception that aggregate studies lack analytic power is a major misconception since there are no logical barriers to the formulation of hypotheses at the level of aggregate data. These studies, in fact, can test hypotheses at a more complex level of determination.

When it comes to a more comprehensive level, there would be no room for the isolation of component vari-

ables from causal models, based solely on the biology of individuals. The ecological design is one of the few models qualified to test hypotheses regarding contextual or macrosocial health processes [124, 152]. A population area or an institution can synthesize an enormous set of variables and processes, with a high degree of complexity, approaching the ecological study of social reality, when the study seeks to apprehend such complexity. If we take this reasoning to its extreme logical consequences, we can conclude that, in this case, it does not make sense to think that the 'ecological fallacy' is necessarily a 'mistake' to be avoided or controlled. On the contrary, it is a feature that facilitates the study of aggregates, a unique identity in the methodological repertoire of epidemiology – provided that due caution is taken not to extrapolate spurious interpretations to individuals. For this reason, following the argument developed by Castellanos [76], it is proposed to call it an 'aggregate effect' instead of an 'ecological fallacy'.

A revaluation of 'descriptive' drawings has also been observed, with an extended perspective, in parallel with the recognition of serious epistemological and methodological problems in classic experimental research models. According to Grimes and Schulz [153], well-conducted descriptive studies are precisely the first scientific basis for new areas of research, providing valuable inputs for generating hypotheses, describing mechanisms and analysing trends in emerging research subjects.

In this line of reasoning, a comparative review of research results, considering several clinical procedures, found no favourable evidence to the superiority of the randomized controlled experimental model over the models of flexible experimental designs or observational studies [154]. Increasingly, the conditions 'written in stone' for classical experimental models taken as gold standards have been questioned, such as randomization of groups and the guarantee of double-blind controls, and are giving way to greater participation of patients in the research process [155].

As an example of the debate about the gold standard represented by randomized clinical trials in the generation of evidence on oral health, a recent study [156] considered limited evidence of any positive effect of the use of cavity-prevention sealants. Nevertheless, the study's outcome of meta-analysis has shown a relative reduction of risk, ranging from 4% to 54% for single applications and 69% to 93% for repeated applications. This article merited the following consideration by Ismail [157]: 'This systematic review focused closely on what constitutes evidence, and its conclusions are not consistent with the results presented. Not all the problems of humanity can be solved with controlled clinical trials'.

21.7 Conclusion

As Susser [158] has stated, epidemiological science is humanitarian in its traditional values. Its objectives go beyond satisfying scientists' intellectual curiosity, the statistical needs of governments or the evidence for clinical practice or planning/evaluation of public health interventions. It is inextricably linked with the social sciences, with collective health, with quantitative and qualitative methods, and with clinical disciplines. Using a cliché, one could say that epidemiology is for society, just as the health professional is for its 'patient'. In this sense, epidemiology cannot take an anti-human or antisocial stance without perversely subverting its own history.

The training of students in oral epidemiology will require conscious induction through the learning of their traditions and history. They will need to feel and understand, through direct experience of the family and community context, the immeasurable drama of avoidable disease and premature death and the wastes of potential that strike entire populations living in deprivation or under the burden of social isolation. They will need to recognize the true scale of pain and suffering indicated by a few percentage points in an epidemiological indicator – such as dental cavities, periodontal disease, dental pain or traumatic dental injuries – for an entire nation. Most of all, they will need to understand that in underprivileged societies, a noble mission of epidemiology is to study and propose solutions for the prejudices that make lives short, unhealthy and unhappy, and increase the pain, suffering and violence that destroys relationships between human beings born in the same society, but in different classes. Injustice harms not only the poorest groups in society but entire societies, so one needs to identify an important point of contact between the literature on inequalities in oral health and the sociology of power [159, 160]. Finally, to understand through study and practice, that although there are different conceptions of epidemiology, it is possible that an all-encompassing point of view prevails. A schism between the extremes of ecosocial epidemiology and molecular epidemiology, with the epidemiology of individual risk factors in the crossfire, cannot be productive.

As Ashton [5] and Buck [161] have pointed out, there should be room in the 'epidemiological imagination and adventure' for anything that contributes to advancing the cause of collective health, such as a deeper understanding of the influences of society, individual risk factors and biochemical mechanisms, providing it is well used and integrated for the sake of human health.

Point of Emphasis

- According to the ecosocial view, social health inequities constitute the defining problem of epidemiology. Hence, two hypotheses have been systematically tested in the literature. The first is that there is a socioeconomic gradient of health that extends across the social scale. The second is that area and context of life is of great importance in ecosocial epidemiology, as they generate health pressures so that people are understood in their broader circumstances.
- With regard to education, prevention and health promotion, research should be encouraged not only on proximal factors considered to be subject to intervention by the health system or the efforts of individuals but also on far-reaching mesial and distal determinants of health that can only be altered by broader social actions.
- Two fallacies or limitations should be avoided in oral health research. The 'individualistic fallacy' which presupposes that individual data are sufficient to explain group phenomena. The 'ecological fallacy', which results from the confusion in the data grouping process, where the spurious interpretation of results based on averages and aggregated data does not necessarily reflect the concrete experience lived by individuals.

References

1. Kuhn TS. The road since structure. Philosophical Essays 1970-1993. In: Conant J, Haugeland J, editors. Chicago: The University of Chicago Press; 2000.
2. Nunes ED. História e paradigmas da Saúde Coletiva: registro de uma experiência de ensino. Cien Saude Colet. 2011;16(4):2239–43.
3. Almeida Filho N. O conceito de saúde: ponto-cego da epidemiologia? Rev Bras Epidemiol. 2000;3:4–20.
4. Jayasinghe S. Conceptualising population health: from mechanistic thinking to complexity science. Emerg Themes Epidemiol. 2011;8(1):2.
5. Ashton J, editor. The epidemiological imagination: a reader. 1st ed. Buckingham, Philadelphia: Open University Press; 1994.
6. Kroeger A, Montoya-Aguilar C, Bichmann W, Gorgen R, Diaz SJ. The use of epidemiology in local health planning: a training manual. 1st ed. London, NJ: Zed Books; 1997.
7. Barreto ML, Almeida Filho N, Veras RP, Barata RB, editors. Epidemiologia, serviços e tecnologias em saúde. Rio de Janeiro: FIOCRUZ, ABRASCO; 1998.
8. Paim JS. Epidemiology and planning: the recomposition of the epidemiological practices in management of SUS. Cien Saude Colet. 2003;8(2):557–67.
9. Veras RP, Barreto ML, Almeida Filho N, Barata RB, editors. Epidemiologia: contextos e pluralidade. Rio de Janeiro: FIOCRUZ, ABRASCO; 1998.
10. Antunes JLF. Socioeconomic status and health: a discussion of two paradigms. Rev Saude Publica. 2008;42(3):562–7.
11. Almeida Filho N, Barreto ML, Veras RP, Barata RB, editors. Teoria epidemiológica hoje: fundamentos, interfaces, tendências. Rio de Janeiro: FIOCRUZ, ABRASCO; 1998.
12. Poole C, Rothman KJ. Our conscientious objection to the epidemiology wars. J Epidemiol Community Health. 1998;52:613–4.
13. Breilh J. Latin American critical ("Social") epidemiology: new settings for an old dream. Int J Epidemiol. 2008;37(4):745–50.
14. Breilh J. Epidemiologia: economia, política e saúde. São Paulo: Editora da UNESP/Hucitec; 1991.
15. Breilh J, Granda E. Epidemiologia y contrahegemonia. Soc Sci Med. 1989;28(11):1121–7.
16. Silva JB, Barros MBA. Epidemiology and inequality: notes on theory and history. Rev Panam Salud Publica. 2002;12(6):375–83.
17. Subramanian SV, Jones K, Kaddour A, Krieger N. Revisiting Robinson: the perils of individualistic and ecologic fallacy. Int J Epidemiol. 2009;38(2):342–60; author reply 370–3.
18. Glass TA, McAtee MJ. Behavioral science at the crossroads in public health: extending horizons, envisioning the future. Soc Sci Med. 2006;62(7):1650–71.
19. Berkman LF. Seeing the forest and the trees: new visions in social epidemiology. Am J Epidemiol. 2004;160(1):1–2.
20. Susser M. Choosing a future for epidemiology: I. eras and paradigms. Am J Public Health. 1996;86(5):668–73.
21. Susser M. Choosing a future for epidemiology: II. From black box to Chinese boxes and eco-epidemiology. Am J Public Health. 1996;86(5):674–7.
22. Haack S. An epistemologist among the epidemiologists. Epidemiology. 2004;15(5):521–2.
23. Krieger N. Ladders, pyramids and champagne: the iconography of health inequities. J Epidemiol Community Health. 2008;62(12):1098–104.
24. Krieger N. Proximal, distal, and the politics of causation: What's level got to do with it? Am J Public Health. 2008;98(2):221–30.
25. Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. Int J Epidemiol. 2001;30(4):668–77.
26. Krieger N. Historical roots of social epidemiology: socioeconomic gradients in health and contextual analysis. Int J Epidemiol. 2001;30:899–903.
27. Lilienfeld AM, Lilienfeld DE. Epidemiology and the public health movement: a historical perspective. J Public Health Policy. 1982;3:140–9.
28. Susser M. Epidemiology in the United States after World War II: the evolution of technique. Epidemiol Rev. 1985;7:147–77.
29. Susser M. Does risk factor epidemiology put epidemiology at risk? Peering into the future. J Epidemiol Community Health. 1998;52:608–11.
30. Renton A. Epidemiology and causation: a realist view. J Epidemiol Community Health. 1994;48:79–85.
31. Mackenbach JP. Public health epidemiology. J Epidemiol Community Health. 1995;49:333–4.
32. Krieger N, Zierler S. What explains the public's health? - A call for epidemiologic theory. Epidemiology. 1996;7(1):107–9.
33. Nakajima H. Epidemiology and prospects for health in the twenty-first century. J Epidemiol. 1996;6(4 (Supplement)):5–10.
34. Savitz DA. The alternative to epidemiologic theory: whatever works. Epidemiology. 1997;8(2):210–2.
35. Bhopal R. Paradigms in epidemiology textbooks: in the footsteps of Thomas Kuhn. Am J Public Health. 1999;89(8):1162–5.
36. Krieger N. Sticky webs; hungry spiders; buzzing flies; and fractal metaphors: on the misleading juxtaposition of "risk factor" versus "social" epidemiology. J Epidemiol Community Health. 1999;53:678–80.
37. Savitz DA, Poole C, Miller WC. Reassessing the role of epidemiology in public health. Am J Public Health. 1999;89(8):1158–61.
38. Buchanan D. Social epidemiology. In: Berkman, LF, Kawachi I, editors. New York: Oxford University Press; 2000. p. 391.
39. Zhang FF, Michaels DC, Mathema B, Kauchali S, Chatterjee A, Ferris DC, et al. Evolution of epidemiologic methods and

concepts in selected textbooks of the 20th century. Soz Praventivmed. 2004;49(2):97–104.
40. Foxman B, Group aTESL. Challenges of epidemiology in the 21st century: comments from the leaders of several epidemiology associations. Ann Epidemiol. 2005;15(1):1–4.
41. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Q. 2005;83(4):731–57.
42. Venkatapuram S, Marmot M. Epidemiology and social justice in light of social determinants of health research. Bioethics. 2009;23(2):79–89.
43. Cameron D, Jones IG. John Snow, the Broad Street pump and modern epidemiology. Int J Epidemiol. 1983;12(4):393–6.
44. Snow J. Sobre a maneira de transmissão do cólera. São Paulo-Rio de Janeiro: Hucitec/ABRASCO; 1990.
45. Rothman KJ. The rise and fall of epidemiology, 1950-2000 A.D. Int J Epidemiol. 2007;36(4):708–10.
46. Bingham P, Verlander NQ, Cheal MJ. John Snow, William Farr and the 1849 outbreak of cholera that affected London: a reworking of the data highlights the importance of the water supply. Public Health. 2004;118(6):387–94.
47. Whitehead M. William Farr's legacy to the study of inequalities in health. Bull World Health Organ. 2000;78(1):86–7.
48. Carpenter M. William Farr: a pioneer of public health. Nurs Times. 1983;79(24):9–11.
49. Langmuir AD. William Farr: founder of modern concepts of surveillance. Int J Epidemiol. 1976;5(1):13–8.
50. Susser M, Adelstein A. An introduction to the work of William Farr. Am J Epidemiol. 1975;101(6):469–76.
51. Engels F. The condition of the working-class in England. London: Granada Publishing Ltd; 1969.
52. Barata RB. Social epidemiology. Rev Bras Epidemiol. 2005;8(1):7–17.
53. Susser M, Stein Z. Eras in epidemiology: the evolution of ideas. Oxford; New York: Oxford University Press; 2009.
54. Oppenheimer GM, Susser E. Invited commentary: the context and challenge of von Pettenkofer'scontributions to epidemiology. Am J Epidemiol. 2007;166(11):1239–41; discussion 1242–3.
55. Piel G, Osborn Segerberg J, editors. The world of René Dubos : a collection from his writings. 1st ed. New York: H. Holt and Co; 1990.
56. Leavell HR, Clark EG. Preventive medicine for the doctor in his community: an epidemiologic approach. New York, Toronto, London: McGraw-Hill Book Company; 1958.
57. MacMahon B, Trichopoulos D. Epidemiology; principles and methods. 2nd ed. Boston, New York, Toronto, London: Little, Brown and Company; 1996.
58. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? Soc Sci Med. 1994;39(7):887–903.
59. McMichael AJ. Prisoners of the proximate: loosening the constraints on epidemiology in an age of change. Am J Epidemiol. 1999;149(10):887–97.
60. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14(1):32–8.
61. Rose G. The strategy of preventive medicine. 1st ed. Oxford, New York, Tokyo: Oxford University Press; 1993.
62. Rose G. Rose's strategy of preventive medicine. New York: Oxford University Press; 2008.
63. Singh A, Harford J, Peres MA. 2018. Investigating societal determinants of oral health-opportunities and challenges in multilevel studies. Community Dent Oral Epidemiol. 2018;46(4):317–27.
64. Batchelor P, Sheiham A. The limitations of a "high-risk" approach for the prevention of dental caries. Community Dent Oral Epidemiol. 2002;30(4):302–12.
65. Batchelor PA, Sheiham A. The distribution of burden of dental caries in schoolchildren: a critique of the high-risk caries prevention strategy for populations. BMC Oral Health. 2006;6(3):1–22.
66. Krieger N. Questioning epidemiology: objectivity, advocacy, and socially responsible science. Am J Public Health. 1999;89(8):1151–3.
67. March D, Susser E. The eco- in eco-epidemiology. Int J Epidemiol. 2006;35(6):1379–83.
68. Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. Int J Epidemiol. 1989;18(1):269–74.
69. Humphreys K, Carr-Hill R. Area variations in health outcomes: artefact or ecology. Int J Epidemiol. 1991;20(1):251–8.
70. Brenner H, Savitz DA, Jockel K-H, Greenland S. Effects of nondifferential exposure misclassification in ecologic studies. Am J Epidemiol. 1992;135(1):85–95.
71. Cohen BL. In defense of ecologic studies for testing a linear-no threshold theory. Am J Epidemiol. 1994;139(8):765–8.
72. Greenland S, Robins J. Ecologic studies - biases, misconceptions, and counterexamples. Am J Epidemiol. 1994;139(8):747–60.
73. Piantadosi S. Ecologic biases. Am J Epidemiol. 1994;139(8):761–4.
74. Greenland S, Robins J. Accepting the limits of ecologic studies: Drs. Greenland and Robins reply to Drs. Piantadosi and Cohen. Am J Epidemiol. 1994;139(8):769–71.
75. Plummer M, Clayton D. Estimation of population exposure in ecological studies. J R Stat Soc B. 1996;58(1):113–26.
76. Castelhanos PL. O ecológico na epidemiologia. In: Almeida Filho N, Barreto M, Veras R, Barata R, editors. Teoria epidemiológica hoje - fundamentos, interfaces e tendências. Rio de Janeiro: Editora FIOCRUZ/ABRASCO; 1998. p. 129–48.
77. Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiol. 1991;133(7):635–48.
78. Rosen G. Uma história da saúde pública. 1a. ed. São Paulo: Hucitec, Editora Unesp, ABRASCO; 1994.
79. Gordon JE. The twentieth century - yesterday, today and tomorrow (1920). In: Winslow C-E, Smillie WG, Doull A, editors. The history of American epidemiology. St. Louis: The CV Mosby Co; 1952. p. 114–67.
80. Ryle JA. Changing disciplines. London: Oxford University Press; 1948.
81. Breilh J. Epidemiologia crítica: ciência emancipadora e interculturalidade. Rio de Janeiro: Editora Fiocruz; 2006.
82. Laurell AC. Social analysis of collective health in Latin America. Soc Sci Med. 1989;28(11):1183–91.
83. Krieger N. Latin American social medicine: the quest for social justice and public health. Am J Public Health. 2003;93(12):1989–91.
84. Ayres JRCM. Sobre o risco: para compreender a epidemiologia. São Paulo: HUCITEC; 1997.
85. Almeida Filho N. A clínica e a epidemiologia. 1a. ed. Salvador - Rio de Janeiro: APCE/ABRASCO; 1992.
86. Marmot MG, Bell RG. Improving health: social determinants and personal choice. Am J Prev Med. 2011;40(1 Suppl 1):S73–7.
87. Bambra C, Smith KE, Garthwaite K, Joyce KE, Hunter DJ. A labour of Sisyphus? Public policy and health inequalities research from the Black and Acheson Reports to the Marmot Review. J Epidemiol Community Health. 2011;65(5):399–406.
88. Marmot M, (Chair). Fair society, healthy lives (The Marmot review): strategic review of health inequalities in England post-2010. London: Marmot Review; 2010.
89. Marmot M. The causes of the causes. Health Serv J. 2009;119(6152):12.
90. Marmot M. Closing the health gap in a generation: the work of the Commission on Social Determinants of Health and its recommendations. Glob Health Promot. 2009;(Suppl 1):23–7.
91. Marmot M. Achieving health equity: from root causes to fair outcomes. Lancet. 2007;370(9593):1153–63.

92. Marmot M. The social pattern of health and disease. In: Blane D, Brunner E, Wilkinson R, editors. Health and social organization; towards a health policy for the twenty-first century. London: Routledge; 1996. p. 42–67.
93. Galea S, Riddle M, Kaplan GA. Causal thinking and complex system approaches in epidemiology. Int J Epidemiol. 2010;39(1):97–106.
94. Bhopal R. Seven mistakes and potential solutions in epidemiology, including a call for a World Council of Epidemiology and Causality. Emerg Themes Epidemiol. 2009;6:6.
95. Berkman LF. Social epidemiology: social determinants of health in the United States: are we losing ground? Annu Rev Public Health. 2009;30:27–41.
96. Mutaner C, Chung HJ. Psychosocial epidemiology, social structure, and ideology. J Epidemiol Community Health. 2005;59(7):540–1.
97. Kaplan GA. What's wrong with social epidemiology, and how can we make it better? Epidemiol Rev. 2004;26(1):124–35.
98. Berkman LF. Introduction: seeing the forest and the trees - from observation to experiments in social epidemiology. Epidemiol Rev. 2004;26(1):2–6.
99. Marmot MG, Wilkinson RG. Social determinants of health. New York: Oxford University Press; 2006.
100. Feinstein AR. Scientific standards in epidemiologic studies of the menace of daily life. Science. 1988;242(4883):1257–63.
101. Susser E. Eco-epidemiology: thinking outside the black box. Epidemiology. 2004;15(5):519–20.
102. Skrabanek P. The emptiness of the black box. Epidemiology. 1994;5(5):553–5.
103. Skrabanek P. The poverty of epidemiology. Perspect Biol Med. 1992;35(2):182–5.
104. Breslow NE. Are statistical contributions to medicine undervalued? Biometrics. 2003;59(1):1–8.
105. Greenland S, Gago-Dominguez M, Castelao JE. The value of risk-factor ("black-box") epidemiology. Epidemiology. 2004;15(5):529–35.
106. Weiss NS. Presents can come in black boxes, too. Epidemiology. 2004;15(5):525–6.
107. McPherson K. Wider. Causal thinking in the health sciences. J Epidemiol Community Health. 1998;52:612–3.
108. Pearce N. Traditional epidemiology, modern epidemiology, and public health. Am J Public Health. 1996;86(5):678–83.
109. Almeida Filho N. Models of social determination of chronic noncommunicable diseases. Cien Saude Colet. 2004;9(4):865–84.
110. Dankwa-Mullan I, Rhee KB, Williams K, Sanchez I, Sy FS, Stinson N Jr, et al. The science of eliminating health disparities: summary and analysis of the NIH Summit Recommendations. Am J Public Health. 2010;100(S1):S12–8.
111. Berkman LF, Kawachi I, editors. Social epidemiology. 1st ed. Oxford, New York: Oxford University Press; 2000.
112. Evans RG, Barer ML, Marmor TR, editors. Why are some people healthy and others not? The determinants of health of populations. 1st ed. New York: Aldine de Gruyter; 1994.
113. Hancock T. Healthcare in the anthropocene: challenges and opportunities. Health Quarterly [Internet]. 2016 [cited 2019 Jan 6];19(3):17–22. Available from: Healthcare in the anthropocene: challenges and opportunities. Health Quarterly [Internet]. 2016 [cited 2019 Jan 6];19(3):17–22. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27808018.
114. Arnold KF, Harrison WJ, Heppenstall AJ, Gilthorpe MS. DAG-informed regression modelling, agent-based modelling and microsimulation modelling: a critical comparison of methods for causal inference. International Journal of Epidemiology [Internet]. 2018 Dec 5 [cited 2019 Jan 6]; Available from: https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyy260/5231935.
115. Last JM, editor. A dictionary of epidemiology. 3rd ed. New York, Oxford, Toronto: Oxford University Press; 1995.
116. Hill AB, Hill ID. Bradford Hill's principles of medical statistics. 12th ed. London Sydney, Auckland: Edward Arnold; 1991.
117. Diez-Roux AV. Bringing context back into epidemiology: variables and fallacies in multilevel analysis. Am J Public Health. 1998;88(2):216–22.
118. Diez-Roux AV. Multilevel analysis in public health research. Annu Rev Public Health. 2000;21(1):171–92.
119. Lynch J, Smith GD, Harper S, Hillemeier M, Ross N, Kaplan G, et al. Is income inequality a determinant of population health? Part 1. A systematic review. Milbank Q. 2004;82(1):5–99.
120. Pickett KE, Wilkinson RG. Income inequality and health: a causal review. Soc Sci Med. 2015;128:316–26.
121. Singh A, Harford J, Antunes JLF, Peres MA. Area-level income inequality and oral health among Australian adults – a population-based multilevel study. PLoS One. 2018;13(1):e0191438.
122. Marmot M. The influence of income on health: views of an epidemiologist. Health Aff. 2002;21(2):31–46.
123. McMichael AJ. The health of persons, populations, and planets: epidemiology comes full circle. Epidemiology. 1995;6(6):633–5.
124. Schwartz S. The fallacy of the ecological fallacy: the potential misuse of a concept and the consequences. Am J Public Health. 1994;84(5):819–24.
125. Hernan MA. A definition of causal effect for epidemiological research. J Epidemiol Community Health. 2004;58(4):265–71.
126. Moreno-Betancur M, Koplin JJ, Ponsonby AL, Lynch J, Carlin JB. Measuring the impact of differences in risk factor distributions on cross-population differences in disease occurrence: a causal approach. Int J Epidemiol. 2018;47(1):217–25.
127. Vanderweele TJ. Ignorability and stability assumptions in neighborhood effects research. Stat Med. 2008;27(11):1934–43.
128. Porta M, Alvarez-Dardet C. Epidemiology: bridges over (and across) roaring levels. J Epidemiol Community Health. 1998;52:605.
129. Moysés SJ, Moysés ST, Allegretti ACV, Argenta M, Wernek R. Dental fluorosis: epidemiological fiction? Pan Am J Public Health. 2002;12(5):339–46.
130. Dean HT. Endemic fluorosis and its relation to dental caries. Public Health Rep. 1938;53:1443.
131. Newton JT, Bower EJ. The social determinants of oral health: new approaches to conceptualizing and researching complex causal networks. Community Dent Oral Epidemiol. 2005;33(1):25–34.
132. Moysés SJ. The current context for research in public Oral health. Cad Saude Publica. 2008;24(4):718.
133. Sheiham A, Alexander D, Cohen L, Marinho V, Moyses S, Petersen PE, et al. Global oral health inequalities: task group - implementation and delivery of oral health strategies. Adv Dent Res. 2011;23(2):259–67.
134. Singh A, Harford J, Schuch HS, Watt RG, Peres MA. Theoretical basis and explanation for the relationship between area-level social inequalities and population oral health outcomes – a scoping review. SSM - Popul Health. 2016;2:451–62.
135. Pattussi MP, Marcenes W, Croucher R, Sheiham A. Social deprivation, income inequality, social cohesion and dental caries in Brazilian school children. Soc Sci Med. 2001;53(7):915–25.
136. Antunes JL, Junqueira SR, Frazao P, Bispo CM, Pegoretti T, Narvai PC. City-level gender differentials in the prevalence of dental caries and restorative dental treatment. Health Place. 2003;9(3):231–9.
137. Moysés ST, Moysés SJ, Watt RG, Sheiham A. Associations between health promoting schools policies on some indicators of oral health. Health Promot Int. 2003;18(3):209–18.

138. Peres MA, Fernandes LS, Peres KG. Inequality of water fluoridation in Southern Brazil - the inverse equity hypothesis revisited. Soc Sci Med. 2004;58:1181–9.
139. Peres MA, de Oliveira Latorre Mdo R, Sheiham A, Peres KG, Barros FC, Hernandez PG, et al. Social and biological early life influences on severity of dental caries in children aged 6 years. Community Dent Oral Epidemiol. 2005;33(1):53–63.
140. Celeste RK, Fritzell J, Nadanovsky P. The relationship between levels of income inequality and dental caries and periodontal diseases. Cad Saude Publica. 2011;27(6):1111–20.
141. Peres MA, Peres KG, Frias AC, Antunes JL. Contextual and individual assessment of dental pain period prevalence in adolescents: a multilevel approach. BMC Oral Health. 2010;10:20. Available from: https://bmcoralhealth.biomedcentral.com/articles/10.1186/1472-6831-10-20.
142. Moreira RS, Nico LS, Barrozo LV, Pereira JC. Tooth loss in Brazilian middle-aged adults: multilevel effects. Acta Odontol Scand. 2010;68(5):269–77.
143. Celeste RK, Nadanovsky P. How much of the income inequality effect can be explained by public policy? Evidence from oral health in Brazil. Health Policy. 2010;97(2-3):250–8.
144. Celeste RK, Nadanovsky P, Ponce de Leon A, Fritzell J. The individual and contextual pathways between oral health and income inequality in Brazilian adolescents and adults. Soc Sci Med. 2009;69(10):1468–75.
145. Pattussi MP, Hardy R, Sheiham A. The potential impact of neighborhood empowerment on dental caries among adolescents. Community Dent Oral Epidemiol. 2006;34(5):344–50.
146. Antunes JL, Peres MA, Jahn GM, Levy BB. The use of dental care facilities and oral health: a multilevel approach of schoolchildren in the Brazilian context. Oral Health Prev Dent. 2006;4(4):287–94.
147. Antunes JL, Peres MA, de Campos Mello TR, Waldman EA. Multilevel assessment of determinants of dental caries experience in Brazil. Community Dent Oral Epidemiol. 2006;34(2):146–52.
148. Moyses SJ, Moyses ST, McCarthy M, Sheiham A. Intra-urban differentials in child dental trauma in relation to healthy cities policies in Curitiba, Brazil. Health Place. 2006;12(1):48–64.
149. Morgenstern H. Uses of ecologic analysis in epidemiologic research. Am J Public Health. 1982;72(12):1336–47.
150. Morgenstern H. Ecologic studies. In: Rothman KJ, Greenland S, editors. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Rave Publishers; 1998. p. 459–80.
151. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998.
152. Schwartz S, Susser E, Susser M. A future for epidemiology? Annu Rev Public Health. 1999;20(1):15–33.
153. Grimes DA, Schulz KF. Descriptive studies: what they can and cannot do. Lancet. 2002;359(9301):145–9.
154. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf. J Clin Epidemiol. 2001;54(6):541–9.
155. Gross D, Fogg L. Clinical trials in the 21st century: the case for participant-centered research. Res Nurs Health. 2001;24:530–9.
156. Mejare I, Lingstrom P, Petersson LG, Holm AK, Twetman S, Kallestal C, et al. Caries-preventive effect of fissure sealants: a systematic review. Acta Odontol Scand. 2003;61(6):321–30.
157. Ismail AI. Visual and visuo-tactile detection of dental caries. J Dent Res. 2004;83 Spec No C:C56–66.
158. Susser M. Epidemiology today: a thought-tormented world. Int J Epidemiol. 1989;18(3):481–8.
159. Wilkinson R, Pickett K. The spirit level: why more equal societies almost always do better. London: Allen Lane, Penguin Books; 2009.
160. Gibson LB, Blake M, Baker S. Inequalities in oral health: the role of sociology. Community Dent Health. 2016 Jun;33(2):156–60.
161. Buck C, Llopis A, Najera E, Terris M, editors. The challenge of epidemiology: issues and selected readings. Washington: Pan American Health Organisation, Regional Office of the WHO; 1989.

Use of Primary Care Settings to Collect Epidemiological Data

Gill Davies and Iain A. Pretty

Contents

22.1 Introduction – 348

22.2 Traditional Epidemiological Methods – 348

22.3 The Use of Primary Care as a Source of Epidemiological Data – 349

22.3.1 The Inherent Bias within Primary Care Data – 349

22.3.2 Accessing Data Routinely Collected by Dentists as Part of Their Assessment and Treatment of Patients – 350

22.3.3 Asking Dentists to Collect Additional Data from Patients During Their Treatment and Assessment of Patients: Using the Primary Care Workforce – 350

22.3.4 Using Primary Dental Care Premises to Access Patients by External Clinical or Non-clinical Staff for the Purpose of Capturing Epidemiological Data – 352

22.3.5 Using Primary Dental Care Sites to Recruit Subjects to Self-report Epidemiological Data. The Role of Technology in Primary Care Data Collection – 353

22.4 Connected Devices and Primary Care Recruitment and Data Triangulation – 354

22.5 Routine Data Collection: Hypothesis Generating or Service Informing – 354

22.6 Conclusions – 354

References – 354

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_22

Learning Objectives

- Describe the features of traditional epidemiological surveys methods for oral health
- Describe the methods of data collection associated with primary care, including benefits and limitations
- Consider the potential of emerging technology to facilitate collection of epidemiological data from primary care

22.1 Introduction

Primary care (defined as healthcare provided in the community for people making an initial approach to a medical practitioner or clinic for advice or treatment) potentially offers a rich source of population level, epidemiological data to inform service commissioners, public health bodies and others with an interest in dental health. There is increasing interest in exploring a variety of approaches which capture oral health data using these settings as an alternative to, or supplementary to, more traditional epidemiological surveys. There are shortcomings and advantages for dental epidemiological surveys which are carried out in community settings and those that are based in primary care.

This chapter looks at the problems that exist in carrying out large scale, traditional epidemiological surveys and then examines the potential uses for primary care in sourcing epidemiological data and the risks and benefits of doing so. Examples for both methods are mainly taken from the current systems in England.

22.2 Traditional Epidemiological Methods

Traditionally dental epidemiology has been carried out in order to establish population level estimates of disease and related factors. This has been achieved for children in England and the rest of the UK by running standardised surveys using schools as sampling units and the sites for clinical examinations and questionnaires [1]. Where such surveys have been run nationally, with all types of school being included in the population sampling frame, this method has had the benefit of access to almost 100% of the population and great efficiency on the part of the fieldwork teams.

The method requires legislation, instigation and funding at governmental level, an agency to ensure national coordination and the development and application of standardised methods, a network of trained and calibrated clinicians, administrative support for these and the cooperation of schools, parents and children. This method is suitable for collecting information on specified population groups, particularly birth cohorts. Such infrastructure may be difficult to establish and maintain, even in countries with well-developed public health approaches and collectively funded healthcare.

Surveys run in schools can provide information on the whole population of an age cohort or a good representative sample of it. Standardisation allows safe comparison and provides a benchmark to allow observation of trends over time if the surveys are repeated with the same methods.

Bias may arise if some areas, types of school or groups of children are not included, for example if some regions or smaller local areas do not take part, perhaps because of refusal, inaccessibility or lack of resources. Some types of school may not be willing to cooperate and so exclude particular types of pupil. For instance, particular faith schools may decline. Finally, bias may be introduced by the requirement for consent, such that the parents of children with higher levels of disease, for example, are less likely to provide consent [2, 3].

Where these biases are overcome, the information arising from such surveys can be invaluable to government, policy makers, commissioners and developers of services, workforce planners and trainers, dental schools and those involved in the instigation and evaluation of oral health improvement interventions. Standardised methods that hold true over many years can provide robust and comparable data which is suitable for observing time trends and making comparisons of a variety of oral health conditions between and within various geographic areas and population groups.

The school-based method may be challenged by structural change arising from changes in government policy or reorganisation of health services and is, by its very nature, restricted to children and adolescents. A variety of barriers are faced by those wanting to establish population levels of oral disease among other population groups as most are not conveniently and consistently grouped together in locations which are conducive to undertaking surveys.

Current healthcare systems, however they may be funded, are short of resource, and there is a risk that traditional epidemiological surveys may be considered too expensive, time-consuming and workforce reliant. There may be problems in maintaining sufficient numbers of trained and calibrated examiners who are able and willing to participate in epidemiological surveys, which often involve extensive travel and time away from both clinical base and also home.

Training and calibrating examiners is time-consuming and expensive, and the availability of reference examiners may be limited, especially in those indices that are less commonly used. As a result, there could be a restriction to the range of conditions examined in epidemiological surveys. For example it has been

over a decade since orthodontic condition was measured in the US NHANES survey.

Access to adult populations is problematic and cannot use the same methods as for child surveys. Sample sizes for surveys of adults may need to be larger than for children as they present an increasingly heterogeneous population. Because of the restrictions in access, there has been an emphasis on care home residents (again due to the relative ease of access and the efficiencies of examining within a single centre) although they represent only a small proportion of older adults in the population. The UK decennial Adult Dental Health Survey is an exception to this and has provided population level information on a variety of oral health conditions from a representative sample of the population [4]. However, the nature of the survey requires face to face contact with adults at home visits for both the questionnaire and clinical examination elements of the survey, and this incurs high costs and limits sample sizes.

22.3 The Use of Primary Care as a Source of Epidemiological Data

There are a range of potential methods for using primary dental care settings to acquire epidemiological data:

(a) Accessing data routinely collected by general dental practitioners as part of their assessment and treatment of patients
(b) Asking general dental practitioners or someone within their clinical team to collect additional data from patients during their treatment and assessment of patients
(c) Using the primary care estate and population base to access patients who are assessed by external clinical or non-clinical staff for the purpose of collecting epidemiological data
(d) Using primary care sites to recruit subjects to self-report epidemiological data through the use of digital means for questionnaires, or other self-directed methods of image or other data capture that may be developed in the future

Each of these will be described in detail in subsequent sections of the chapter.

22.3.1 The Inherent Bias within Primary Care Data

The potential for collecting data from primary care settings may be a very appealing alternative to community-based population surveys, but there is an underlying issue with each of the approaches – that of bias. Using primary care resources will, inevitably, bias the collection of data as they are being sourced from individuals who *attend services*. This bias needs to be both recognised and considered in the light of:

(a) Methods of funding care as this varies widely from one country to another. Where dental treatment services are funded in full or in part by taxation or a national insurance scheme, then people from most sectors of the population may attend for care. In other circumstances where individuals are responsible for paying for their own treatment, there may be a large bias, with more deprived sectors unable to afford care. This financially linked attendance bias could be a large limitation to use of data generated in the primary care setting.
(b) The scale and duration of data collection, where this is long term, and for large numbers of the population, attendance bias may be of less concern. For example, by accessing the data of all patients who attended practices in a city over a period of 10 years, it is likely that a large proportion of the population will have attended, if only for symptomatic relief or referral. The oft-quoted figures of 50% adult attendance at practices in the UK are generally over a 2-year period, and over longer periods, this rises dramatically. In the 2009 Adult Dental Health Survey, 98% of respondents, who had been recruited from their home addresses alone, stated that they had used dental treatment services at some time [4].

    If large samples are accessed, then even those who are rare attenders are likely to be represented and their oral health status established. It may be hypothesised that their oral health and service use may be very similar to non-attenders and so give sufficient insight into that elusive group.
(c) Purpose of the data – if the rationale for collection is the assessment of service use or demand, then attendance bias is largely irrelevant. The prevalence and incidence of many other health conditions are measured solely from among service users, and the potential for under-recording is acknowledged. However, if data are to be extrapolated to a health needs assessment of the whole population, then attendance bias is clearly an issue. Supplementary surveys of non-attending groups may be required to provide a full picture of needs and make comparisons.
(d) Primary care data may be considered as hypothesis generating rather than definitive data, or large routine data sets may be used to confirm, or be supplemented by, smaller traditional epidemiological examinations.

There is therefore a need to accept and recognise the potential for bias and consideration given to how it may be either mitigated or reported correctly to ensure interpretation is appropriate.

22.3.2 Accessing Data Routinely Collected by Dentists as Part of Their Assessment and Treatment of Patients

Primary care data are those collected through the process of routinely examining, treating and reviewing a population of attending patients and seeking financial recompense for doing this. Depending on the country and health service model, as well as national standards of dental record keeping, retention and reporting, these data will be varied. For example, if a data element is required to obtain payment for a treatment, then it is likely that such fields will be accurately completed, whereas non-mandatory clinical information may not. Data can be separated into two broad areas:

(a) Selected data that are sent to national bodies or insurance companies for payment, or regulatory reasons. These are normally an abbreviated or summary of data and tend to relate to a course of treatment rather than a comprehensive treatment record
(b) Full clinical data that are held as part of the patient record and frequently held within practice management systems (software and database solutions).

As an example, in England and Wales, dentists working within the National Health Service (NHS) are required to submit a summary clinical data report (known as an FP17 form) to the NHS Business Service Authority (BSA) in order to receive payment for their work. BSA data can be considered as routinely collected and can be accessed via a number of routes and permission models. High level, fully anonymised population data (accessed without individual consent) are frequently used to map attendance, treatment and service utilisation. However, with the establishment of appropriate consent systems from patients, individual data may be accessed for current and historical information. This would allow perusal of claim histories over many years and potentially many different dental providers. The NHS has been seeking to increase the amount of clinical data supplied with the FP17, and, given the widespread use of practice management systems that automatically populate and submit the FP17, this has been achieved without increases in the burden of data reporting on dentists. As an example, the FP17 record now includes a count of each patient's dt/DT, mt/MT and ft./FT although there has not yet been an assessment of the quality or accuracy of such reporting (Fig. 22.1).

Accessing full patient data via practice management systems potentially provides a richer and more complete picture of an attending population's oral health but requires greater resource for access from both a consent and logistical perspective. Unlike medical general practitioners, who, in the UK at least, use a limited number of practice systems, there are a wide range of providers in the dental space with the UK having around ten systems alone. These are, generally, legacy systems that have developed over many years and, as such, use bespoke data structures, fields and variables. Each will export these to a standard format for the purposes of billing – i.e. completing the FP17 – but will otherwise rely on their internal data dictionaries.

The issue of 'closed' systems has been recognised across health sectors as a considerable impediment to patient care, transfer of data and secondary uses. Many healthcare systems are therefore mandating that software must adopt open standards for data structures, use common variable names and fields (e.g. the use of SnoMed is being widely adopted in the UK, EU and USA) and make data transferrable between systems using standard interface solutions (such as FIHR).

While these developments are taking place in medicine, where data sharing has been established for many years and which, in many ways, underpins much of what is done in primary care, such progress is slower in dentistry. Using practice level data for epidemiology will therefore require, typically, a deep understanding of the export structures of such data, and, as is frequently the case, many data are not exportable, requiring a clinically trained individual to view the records on screen and complete an epidemiological proforma. While extensively used by clinicians, the presence of free text fields is problematic for epidemiologists, requiring human input and translation (Fig. 22.2).

22.3.3 Asking Dentists to Collect Additional Data from Patients During Their Treatment and Assessment of Patients: Using the Primary Care Workforce

This approach uses the general dental practice workforce to collect data from their patients, over and above that routinely collected during examination, treatment, review and billing. There are several levels at which this could be implemented, each requiring differing levels

Fig. 22.1 Advantages and disadvantages of routinely reported data

Advantages
Large data sets with wide population of subjects including adults and children
Standard data reporting fields with no free text and accompanied with a data dictionary
Accessing relatively simple process as anonymised
Clinical data related to actual costs provided
Disadvantages
Can be problematic to send, store and assess securely.
Aggregated data that may obscure areas of interest or levels of granularity required
The need to protect anonymity means that small numbers may be aggregated to prevent possible identification of subjects
Limited information on outcomes, health or other non-billing or non-mandatory items
Costly for clinical teams to provide data and persuasion or incentive would be required for teams to comply
Requires some level of training and agreement of definitions to ensure validity of data reported
Software systems would need to be aligned to improve comparability of data
Infrastructure would need to be established to; agree measures to collect, age groups to include, periodicity required; instigation of standardised system, measurement of validity, collation of arising data, quality control and a reporting and publishing system

Fig. 22.2 Advantages and disadvantages of using practice level data

Advantages
Large data sets with wide population of subjects including adults and children with full demographic details
Full and historical data from attending patients including medical histories and imaging – no data aggregation
This could occur automatically with no additional input required from primary dental care staff
Disadvantages
Will require individual consent to be taken from each patient leading to recruitment bias, and increase in resources required
Lack of consistent data fields across practice systems and extensive use of free text can make coding data complex and time consuming
Software systems would need to be aligned to improve comparability of data
Infrastructure would need to be established to; agree measures to collect, age groups to include, periodicity required; instigation of standardised system, measurement of validity, collation of arising data, quality control and a reporting and publishing system

of training and resource. Practitioners may simply be asked to collect questionnaire data, or simple narrative responses from patients that may be combined with data from the patient record, for example information on smoking cessation or other lifestyle/medical factors. Such an approach takes little in the way of training or additional burden to the practitioner. A further approach is collecting standard dental data but which is not routinely recorded. An example may be caries recording or periodontal status measurements using epidemiological definitions rather than clinician opinions. Such collection and reporting will be generally familiar to general dental practitioners, but there would still be a small burden in recording the outcomes in a standard fashion and the additional clinical examination time. Dentists may require training and some calibration, although the level required cannot be known without further investigation. If 'sentinel' practices or individual clinicians were used for this work, rather than all clinicians being required to do it, the need for widespread and repeated training would be reduced.

The most resource intensive approach is the use of dentists to collect formal epidemiological data using standardised indices that are not routinely used in practice. Examples of this might include the use of a plaque index (such as Turesky) or fluorosis (such as Dean's Index). While the use of such indices improves data quality and enables meta-analyses across practices, it involves significant levels of training and calibration. As such the approach fails to address issues around reference examiners and resources, so while an examiner workforce is accessible, the capacity issues and complexity of training may remain. General dentists are an expensive resource, and their experience in routine examination and treatment may present challenges when asked to assess and record disease or health in other, standardised ways.

The use of technology may offer a solution to the examiner issue. For example, dental clinicians could be supplied with simple, affordable, intra-oral cameras and be asked to collect image data from patients of soft or hard tissues. Using some simple training, these images can be standardised and of high quality. Images collected from practices could be sent to a central area where they can be scored by remote examiners. This decreases examiner requirements, enables reference examiners to score a wider range of images and enables digital calibration and training.

22.3.4 Using Primary Dental Care Premises to Access Patients by External Clinical or Non-clinical Staff for the Purpose of Capturing Epidemiological Data

An alternative to using practice staff is to employ visiting examining teams who are trained to undertake the survey. This approach has been used in both epidemiological surveys (Macey & Pretty) and more formal research projects (Jones, IQuaD). Cooperation of host practices would be required and space and facilities made available. This method would allow the main business of the treatment service to continue, and greater consistency of data collection is likely. Busy practices with multiple clinicians would provide a large pool of potential patient subjects. The disadvantages of using visiting teams are that practices may be unwilling to host them, or some sites may be too small to accommodate them. Patients may be unwilling or unable to take part. The timing of visits by the examining team would have to take into consideration the likely preferred visiting habits of various types of patients so as to maximise the opportunities, although the use of incentives may facilitate patients attending practices on days when they don't have appointments for treatment.

Macey et al. used this approach, combined with imaging technology to study fluorosis in adult populations attending dental practices in England. The approach enabled patients to be recruited based on their lifetime residency, and they were imaged at a routine dental visit. The practices facilitated the survey by ensuring that recall appointments for individuals who were likely to meet the inclusion criteria were booked on the same day. Practices reported enjoying being involved in the process, and recruitment and consent rates were high.

A national study run along similar lines as that described above was coordinated run by Public Health England (PHE, 2019) and was successful in recruiting nearly 17,000 volunteers from adults attending NHS and private practices across the country. A large number of local teams were commissioned and trained to carry out this survey according to a national protocol. The resulting sample matches well with characteristics of the whole adult population with regard to age and social class. Questionnaires were used to gain information about service use, barriers to care and receipt of

preventive advice. Clinicians with training in epidemiology undertook brief examinations in spare surgeries and measured numbers and status of teeth, natural and artificial, posterior contacting pairs, gingival health, presence and status of prostheses and the presence of PUFA conditions. It was recognised that adults with complete upper and lower dentures were under-represented in the sample. The method requires much effort to communicate with general dental practices to ensure cooperation, and the role of local official bodies giving reassurance and encouragement is essential.

22.3.5 Using Primary Dental Care Sites to Recruit Subjects to Self-report Epidemiological Data. The Role of Technology in Primary Care Data Collection

An alternative approach would be for attendees at general dental practices to self-report their responses to questionnaires while at the site, using suitable technology. This would not require a dedicated survey team to be present and would only need the practice receptionist to prompt patients to take part. It may increase the likelihood of participation but could only be limited to non-clinical measures with current technology.

However, technological approaches are being increasingly used in epidemiological studies. A recent review by Hogan outlined the potential uses of imaging, scanning and instrumental techniques to record a wide range of dental conditions, health and disease [5]. These are summarised in Table 22.1. Technology offers the ability to reduce the need for expensive human data collectors, use a wider workforce, increase standardisation, improve governance, undertake longitudinal assessments and revisit data sets for additional assessments. An example is the use of imaging in the assessment of dental fluorosis. This is traditionally a difficult dental feature to measure, and there is a global shortage of trained and calibrated examiners. In order to assess the prevalence and severity of fluorosis in four UK cities (two with water fluoridation and two without), high-resolution images were taken using an extra oral camera by non-dentally qualified personnel [6]. This was undertaken in school settings but could equally easily be dome in primary dental care settings. Images were uploaded and collated, so they could be remotely scored by trained and calibrated examiners in both TF and Dean's Index. This resulted in a rapid data collection process that was not reliant on clinically trained team members and could

Table 22.1 Summary of potential conditions, health and disease states that can be measured using primary care resources

	GDP	Examiner	Imaging/technology-based	Practice level data	Shelf data
Dental caries	Yes	Yes	Yes (depending on site)	Possibly	Possibly
Periodontal diseases	Yes	Yes	Possibly – gingival inflammation	Possibly	No
Malocclusions	Yes	Yes	Yes	Rarely	Demand only
Orofacial pain	Yes	Difficult – low prevalence	No	No	No
Dental fluorosis	Possibly	Yes	Yes	No	No
Dental trauma	Yes	Yes	Yes	Possibly	No
Cleft lip and cleft palate	Yes	Yes – but low prevalence	Yes	Referral data	Secondary care data
Enamel defects	Possibly	Yes	Yes	No	No
Oral cancer	Yes	Yes Low prevalence	Possibly	Referral data	Referral data
Tooth wear	Yes	Yes Low prevalence	Yes	No	No
Tooth loss	Yes	Yes	Yes	Yes	Yes
Halitosis	Yes	Yes	No	No	No
16. Soft tissue lesions	Yes	Yes Low prevalence	Yes	Referral data	Referral data

utilise internationally recognised examiners to score the images. The added benefit was that the examiners were blind to the sites from which the images were taken. The images could then be retained and used, for example, on gingival health or anterior orthodontic condition, as the consent process included these additional examinations.

The advent of whole mouth, colour calibrated, 3D scanning offers the potential for a wide range of dental conditions to be remotely, or even automatically assessed. With scans taking around 5 minutes and within the scope of practices of suitably trained therapists, hygienists or dental nurses, they offer the ability to capture the oral health status of subjects simply and efficiently. With the cost of such scanners decreasing, the ability to place these into primary care settings has become realistic.

22.4 Connected Devices and Primary Care Recruitment and Data Triangulation

There is a significant movement to enable subjects to collect and report their own data using connected and wearable devices. Primary care offers the potential to recruit subjects that meet inclusion criteria and to provide historic dental data which can then be supplemented with subjects' self-submitted data. Connected toothbrushes are one such example of this technology [7]. McKenzie reported that such brushes offer the ability to report not only frequency, duration and timing of brushing but also an assessment of brushing efficacy (based on angulation of brush and zonal coverage within the mouth).

The costs of such devices are decreasing and are also available as add-ons to existing toothbrushes or in manual brushes. There is a risk of bias associated with these technologies – we are unaware of how they might act as an intervention themselves, or that subjects with access to smartphones (usually required to collect data via apps) will represent a segment of the population rather than being representative. However, with over 90% of UK adults having a mobile phone and 77% with a smartphone, this may become irrelevant in the future. Such technologies permit the epidemiologists an insight into the behaviours that might underpin the clinical data that are collected.

22.5 Routine Data Collection: Hypothesis Generating or Service Informing

An approach that can be taken is utilising a mixture of approaches based in primary care. For example, a large data set could be acquired for the purposes of service utilisation assessment and understanding, and then this could be followed by a smaller, more in-depth assessment using patient records at a practice level. For example, McKenzie used BSA data to examine the dental service utilisation of 690,433 older adults living in the North West of England. She was able to report that attendance with a dentist working under NHS contract decreased as age increased, such that 49% of 65- to 74-year olds made an attendance within each 24-month period, compared to only 39% of 75- to 84-year olds and 23% of those over 85 years. She also found that across all age stratifications, the more deprived patients had a higher rate of examinations, extractions, provision of dentures and preventive advice compared to the least deprived patients. These findings can be considered as hypothesis generating – providing initial data that can be used as a basis for further exploration. In the current example, McKenzie went on to access patient level data for over 300 individual older adults by examining their clinical records, with their consent – providing a rich insight into the influence of risk factors in older adults.

22.6 Conclusions

The potential for using data derived from primary dental care settings is vast, especially if this could be linked with wider data sets on health. Technology is currently being developed such that participation by a large number of sites and volunteers will become much less onerous and so improve the representativeness of the sample data collected.

The method will remain limited in its application if the data available is restricted to treatment provision instead of patient need as the two are not equivalent. Multiple steps need to be taken to establish such systems including research about validity and accuracy, the optimum level of training needed and the best approach with regard to all clinical teams being involved or just a few, ongoing data collection or specific surveys on selected groups at agreed times. Data capture systems need to be harmonised, and centralised data analysis systems established, with appropriate power and governance methods, for collating, analysing reporting and interpreting the data. Such structures would need to be set up regardless of the system of funding and providing dental treatment in order for the potential to be realised and maximum yield gained by these various methods of capturing data from primary dental care settings.

References

1. Public Health England. 2018: Oral health survey of 5 year olds 2019: protocol. Gateway number 2018388. www.gov.uk.
2. Daviees GM, Robinson R, Neville J, Burnside G. Investigation of bias related to non-return of consent for a dental epidemiological survey of caries among five year olds. Community Dent Health. 2014;31:21–6.

3. Monaghan NP, Jones SJ. Morgan MZ (2011) do parents of children with caries choose to opt out of positive consent dental surveys in Wales? Br Dent J. 2011 Jan 22;210(2):E1. https://doi.org/10.1038/sj.bdj.2011.26.
4. NHS Information Centre. Adult dental health survey 2009. The Health and Social Care Information Centre, 2011.
5. Hogan R, Goodwin M, Boothman N, Iafolla T, Pretty IA. Further opportunities for digital imaging in dental epidemiology. J Dent. 2018;74(Suppl 1):S2–9.
6. Pretty IA, Boothman N, Morris J, MacKay L, Liu Z, McGrady M, Goodwin M. Prevalence and severity of dental fluorosis in four English cities. Community Dent Health. 2016;33(4):292–6.
7. McKenzie KW, Pretty IA. Connected toothbrushes: bridging the gap to personalized oral health. Am J Dent. 2018;31(3):115–20. PMID: 30028927

Big Data and Machine Learning

Stefan Listl and Alexandre D. P. Chiavegatto Filho

Contents

23.1 Introduction – 358

23.2 "Big Data" – What It Is and Why It Is Useful for Oral Epidemiology – 358

23.3 Challenges of and Methods for Big Data Analytics – 359

23.4 Spurious Correlations – 360

23.5 Causal Methods for Observational Studies – 361
23.5.1 Differences-in-Differences – 361
23.5.2 Regression Discontinuity – 361
23.5.3 Propensity Score Matching – 361
23.5.4 Instrumental Variables – 361

23.6 Machine Learning in Big Data – 362

23.7 Machine Learning Algorithms – 363
23.7.1 Random Forests – 363
23.7.2 Gradient Boosted Trees – 363
23.7.3 Artificial Neural Networks – 363

23.8 Implementation of Big Data Acquisition, Storage, and Processing – 363

23.9 Conclusion – 364

References – 364

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_23

Learning Objectives

- To characterize the generic attributes pertinent to the nature of big data
- To understand the methodological chances and challenges involved in using big data
- To know methods for causal inference using observational data
- To illustrate the principles of machine learning in big data
- To describe requirements for the acquisition, storage, and processing of big data

23.1 Introduction

The term "big data" has recently gained considerable popularity, including in dental research (see, e.g., [3, 8]). However, while it is often referred to as "big data," it remains unclear how this term should be defined exactly. If people use the term "big data" but have different concepts in mind, this may complicate scientific dialogue which should ideally be based on a clear and common understanding of scientific terms and approaches being referred to. Hence, before going into other details, it should first be asked: is it possible to identify a clear definition for the term "big data"? Are there at least some attributes that may help to grasp the nature of "big data"?

23.2 "Big Data" – What It Is and Why It Is Useful for Oral Epidemiology

Various descriptions have been proposed in relation to the term "big data." In line with an earlier description of key characteristics of data management [7, 15], the following three key attributes are specifically pertinent to the nature of big data (also illustrated in Fig. 23.1):

- *Volume:* refers to the amount of data, e.g., from Electronic Health Records, insurance claims data, or mobile sensors. For health and medical data, volume is expected to continue raising substantially and to be routinely measured in terabytes, petabytes, or yottabytes
- *Velocity:* refers to the speed and frequency of data creation, processing, and analysis, which can, e.g., be in the style of batch, near-time, or real-time data usage
- *Variety:* refers to the complexity and heterogeneity of multiple data sources which can be structured, semi-structured, and unstructured

Other attributes have also been proposed to be relevant to characterize the nature of (big) data, in particular [8]:

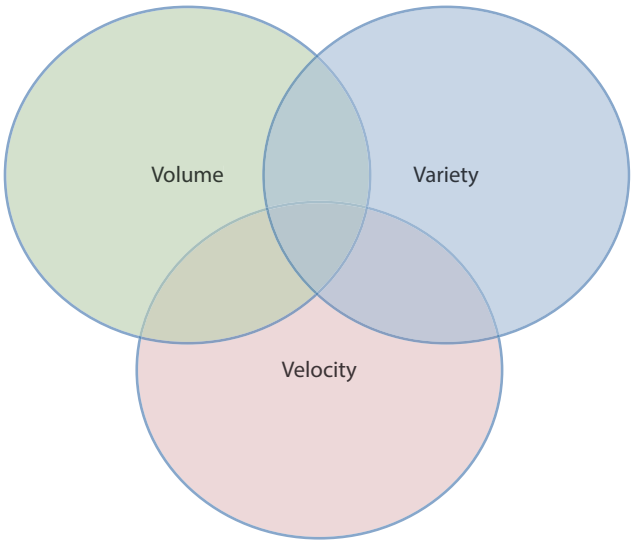


Fig. 23.1 The three key characteristics pertinent to big data

- *Value:* data should be meaningful for the purpose they are being used for.
- *Veracity:* data should be trustworthy, reliable, and verifiable.
- *Variability:* data should be consistent when measuring information over time.

For sake of simplicity, we establish the following working definition for "big data" (see ▶ Box 23.1):

Box 23.1 Working definition for the term "big data"

"Big data" are high-volume data that allow for smart data processing and integration of multiple data sources.

Conventional large-volume data sources which have been used in dental epidemiology research include health interview/examination surveys such as the National Health and Nutrition Examination Survey (NHANES) or the Survey of Health, Ageing and Retirement in Europe (SHARE). Another prominent example is the Global Burden of Disease (GBD) Study which has been integrating and processing input data from multiple data sources to estimate the burden of dental diseases worldwide. Other examples of big data sources amenable to dental research are routinely reported administrative data (e.g., insurance claims data), electronic health records (EHRs), high-resolution imaging data (from dental radiography, magnetic resonance imaging, and computed tomography), genome sequencing data, as well as data collected via smartphone applications

or oral hygiene devices (e.g., PROMs/PREMs or toothbrushes, which track toothbrushing behavior).

Some recent examples from dental research with proximity to "big data" include the following:

- Integration of clinical data, survey data, and genotype data from multiple data sources to examine the extent to which total adiposity is a causal risk factor for periodontitis [23].
- Processing of administrative data and patient self-reported data in an electronic dashboard as visualized feedback information to motivate dental practitioners toward improving quality of care [1].
- Development of an Electronic Decision Support System for enhancement of medical–dental integration [21]. Thereby, automated processing of patient data can be useful to facilitate better alignment between medical and dental care.
- Employing EHRs to detect dental adverse events [14].
- Studies applying machine learning based on artificial neural networks to dental treatment decisions through analysis of electronic health records and dental imaging data [28].
- Analysis of genome sequencing data to identify nucleotide variants as risk loci for periodontitis [18].
- Use of large-volume administrative data to identify the effect of dentists being paid fee-for-service instead of fixed salary payments on the incidence of dental X-raying [2].

The opportunities (and challenges) of big data for epidemiology are expansive [20]. In the field of oral epidemiology, big data can be useful for advancing the study and analysis of the distribution and determinants of oral health and related health conditions. The knowledge derived from oral health related big data analytics can help improve oral health policy and clinical decision making by better specification of intervention points. Use cases for big data in oral epidemiology research include, inter alia:

1. Inference on the causation of oral diseases (including links with other diseases)
2. Oral disease and risk factor surveillance (including high-precision geo-mapping)
3. Impact evaluation of oral health interventions (including clinical and public health)
4. Forecasting of disease patterns into the future (e.g., scenario modeling for demographic changes)
5. Information systems for clinical, public health, and health policy decision makers (e.g., system dynamic models for needs-based workforce planning)

23.3 Challenges of and Methods for Big Data Analytics

Despite the great potential of using big data to improve oral health, there are several challenges that need to be addressed. Overcoming these challenges is critical to ensure that the expectations brought by big data are met and to avoid growing disappointments that may create a lasting barrier to its advancement.

A first crucial challenge is the quality of the data itself. First of all, the use of more data increases the risk of typing errors. The quality of the analyses always depends on the quality of the available data ("garbage in, garbage out"), which means that it is difficult to compensate for errors in the database with statistical models. There is a trade-off that often needs to be addressed between quantity vs. quality, and, in general, it is preferable to sacrifice quantity for quality of the data.

In order to improve data quality in oral health, it is important to promote a virtuous cycle in which those responsible for collecting the data are also involved in research projects that use this data [26]. This engagement allows for a richer appreciation of the data-collecting process and a more careful commitment to the accurate collection of the available information.

Another initial issue is the type of data available to be analyzed. The use of unstructured data, i.e., data that is not presented in a predefined format, is common in big data, as is often the case with images or natural language. This problem can be solved by converting the database to a more suitable format for data analysis in the form of spreadsheets with columns and rows or by directly applying specific methods for this type of data, as in the case of some machine learning techniques such as convolutional and recurrent neural networks [11].

The aggregation of data from different sources will be necessary for the continuous growth of data availability. This will be a particular challenge for clinical oral health as it is historically delivered by small individual practices with very little interconnectivity [22]. Collaborations for the sharing of oral health data will be necessary to guarantee the representativeness of the training samples and to ensure that a sufficient number of examples will be available to improve the quality of the analyses.

Another important challenge will be the difficulty of unifying different classification systems [13]. The tenth Revision of the International Classification of Diseases (ICD-10) was approved in May 1990, but 30 years later, some medical professionals are still struggling to fully

implement the classification in its daily clinical practice [5]. In January 2019, the new version of the International Classification of Diseases (ICD-11) was submitted to the 144th Executive Board Meeting of the World Health Organization and the expectation is that Member States will start reporting ICD-11 on January 2022. This transition can be an interesting test for big data methods, as machine learning algorithms are already being applied for automated ICD coding [25].

23.4 Spurious Correlations

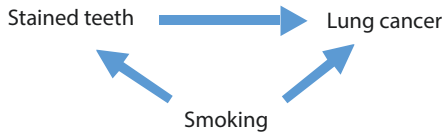
Regarding actual data analysis, the use of big data presents a few challenges for traditional inference problems, mainly due to the existence of spurious associations, which occur when there is a clear mathematical relationship between two variables, but without the presence of a causal relationship [12]. This problem is fairly common when analyzing the relationship between thousands of variables without an initial theoretical selection for variable plausibility. In this case, the probability is high that some of these variables will be statistically correlated due to chance alone. Assuming a real relation in these cases is an issue since the result was purely random and will not be generalizable for future samples, since there is no actual causal relation between them.

The challenge for establishing causality is to find the counterfactual, which is what would have happened to that person if the intervention or factor of interest had not happened. In the presence of a counterfactual, the effect of an intervention is simply the difference in the outcome found with (D_{11}) and without (D_{10}) the treatment.

$$D_{11} = E[Y_i(1)|T_i = 1]$$

$$D_{10} = E[Y_i(0)|T_i = 1]$$

By its very definition, the counterfactual does not exist in the real world, as it is not possible for the same person to receive and not to receive an intervention at the same time, and so it must somehow be approximated. A common, and often misguided, solution is to use the untreated as counterfactual of the treated. However, this could be an issue due to the presence of confounding variables and selection bias. In the case of oral health, an example of confounding variables occurs when the association of stained teeth and lung cancer is tested. A simple association between the two factors may indicate a high correlation, but this is probably due to the presence of a confounding variable such as smoking.



In this case, since smoking is known to be a major cause of stained teeth and lung cancer, people who have stained teeth are more likely to develop lung cancer, but not necessarily because of a direct causal relationship, but because of the effect of a third variable (smoking) in both.

Another issue that impacts causal analysis is the presence of selection bias. When analyzing the impact of an intervention (or risk factor) through an observational study, it is important to consider that people generally self-selected for this intervention, which means that they probably differ in other factors from those who did not have the intervention.

For example, in examining whether a public policy that offers voluntary classes on dental hygiene is associated with the future presence of oral diseases, there may be a statistically significant positive association that is not necessarily causal. People who choose to attend voluntary classes on dental hygiene are likely to have greater interest and concern about their oral health and would already have lower prevalence of illnesses than the rest of the population even if they had not attended the classes. A simple comparison between people who chose and did not choose to attend the classes would therefore lead to incorrect causal conclusions.

The gold standard for inferring causality is conducting a randomized experimental study. By randomly sorting those who will participate in an intervention, it is possible to remove the effect of self-selection, since individual allocation in the intervention or the control groups will be by chance alone. In this case, if the randomization process is carried out correctly and with an adequate number of participants, the intervention and control groups will be on average very similar. In this case:

$$E[Y_i(0)|T_i = 1] = E[Y_i(0)|T_i = 0]$$

That is, although the counterfactual does not actually exist, it can be approximated by a randomized experimental study, since people who did not receive the intervention will be on average very similar to those who received the intervention. The difference in outcomes between the two groups can therefore be considered the causal effect of the intervention.

However, experimental studies have the problem of being costly and time consuming, in addition to the fact that in some cases it may be ethically objectionable. The solution in these cases is the use of causal methods for observational studies, which under some assumptions can simulate the presence of an experimental study.

23.5 Causal Methods for Observational Studies

In cases where a randomized controlled trial is unfeasible or unethical, there are a few causal methods for observational studies that can approach a causal relationship under some assumptions, in order to avoid the common issues of confounding and self-selection in big data analyzes. As more and more data is collected and available for use, there will be more cases where the necessary assumptions are met for the application of these methods. We will briefly cover four of the most common causal methods for observational studies: differences-in-differences, regression discontinuity, propensity score matching, and instrumental variables.

For more insights in methods for causal inference on basis of observational data, the interested reader is recommended to read relevant other literature (see [16] and references therein).

23.5.1 Differences-in-Differences

As the name implies, differences-in-differences are based on a double subtraction. The difference between the posttreatment and pretreatment is first calculated separately for the treated and control group, followed by the difference of the previous result for the two groups.

The main positive point of using differences-in-differences is that it allows for controlling the fixed characteristics of the observations, i.e., those that do not vary in time. The main assumption of differences-in-differences is that the temporal trajectory of the variable of interest is the same for the two groups (intervention and control). This is ensured by identifying similar trajectories between the two groups in the pre-intervention period. If the trajectory is similar in the period before the intervention, it is assumed that had the intervention not occurred, the trajectories would remain similar. Thus, the effect of the intervention is the change in the *trajectory* between the treated and the untreated. An important point here is that it is not necessary for treatment and control groups to start from the same point, only that they are following the same time trend.

23.5.2 Regression Discontinuity

Regression discontinuity is used when there is a discontinuity in the probability of receiving treatment due to the existence of a well-defined eligibility criterion. For example, suppose that all public schools with a family income below $ 20,000 receive classes on oral hygiene, while those above do not. The two groups in general will be very different, but if you compare only the schools that are close to the eligibility criteria, for example, those with income of $ 19,900 and those with income of $ 20,100, the overall differences will not be on average large among the intervention and control groups. It is important that in this case, a descriptive comparison is made of the distribution of the characteristics of the two groups before the intervention, and if this similarity is confirmed, the control group can be considered to be the counterfactual of the intervention group.

23.5.3 Propensity Score Matching

Propensity score matching is the most popular pairing method for analyzing the impact of interventions. Matching techniques seek to find similar pairs of intervention and control groups. The goal here is to find pairs so similar that the only thing that differentiates them is the fact that one received treatment and the other did not. The main hypothesis assumed by this method is that there are no unobserved variables correlated with the treatment outcome. Without the presence of unobserved variables, controlling for all variables associated with the treatment outcome allows us to assume that the treatment effect does not depend on whether or not this observation is in the treatment group.

The propensity score matching, created by Rosenbaum and Rubin, uses a summary of the observed variables that can affect the treatment outcome, which greatly facilitates the matching between control and treatment groups. This summary will be the probability of receiving the treatment given the set of variables X, which is known as the propensity score. The most common way of estimating the propensity score is through a logistic regression where the dependent variable is receiving the intervention or not, and the independent variables are the set of variables that affect the potential outcome.

23.5.4 Instrumental Variables

The instrumental variables approach exploits random variation in a variable (i.e., the "instrument") that impacts on the exposure variable examined, but is not correlated with variations in the outcome or in unobserved confounding variables. Thereby, the instrument must influence the outcome variable only indirectly via the examined exposure variable but not otherwise. For example, a recent study exploited exogenous variation in the duration of schooling as an instrument to detect the causal relationship between education and tooth loss [17].

23.6 Machine Learning in Big Data

Among the structural changes that the analysis of big data will likely bring to health care, one of the most promising is the development of predictive models with artificial intelligence, known as machine learning, that usually need large data sets to achieve a high predictive performance. Machine learning, if based on sound theoretical frameworks and guided by relevant clinical and population health questions, offers vast potential for observational epidemiology [9]. The application of machine learning can help professionals predict the future occurrence of oral diseases, predict risk of oral treatment withdrawal, find similar groupings of patients to test similar interventions, among other possibilities. For example, machine learning may be useful to enhance the development of Clinical Decision Support systems targeted at better integration of medical and dental care [21].

There are four types of machine learning: supervised, unsupervised, semi-supervised, and reinforcement learning. Supervised learning is when there is a label that one wants to predict, which can be either a numerical value (regression) or a category (classification). Non-supervised learning is when there is no label and the goal is to find patterns in the data, such as clustering or performing dimensionality reduction. Semi-supervised learning is a combination of the previous two, usually when you have some data with label and some not. Reinforcement learning has the goal of learning suitable behaviors through an interaction with a dynamic environment that receives feedbacks from rewards and punishments.

The most commonly used in health studies is supervised learning, where models learn structures in the data to make a specific decision, such as diagnosing diseases and predicting the risk of adverse events. A few recent applications of supervised learning in oral health include predicting oral malodor from salivary microbiota [19], classifying patients into aggressive and chronic periodontitis using microbial profiles [6], and detecting tooth caries in bitewing radiographs [24].

Supervised algorithms are divided into two groups according to the type of variable to be predicted. Regression problems are models that try to predict a continuous variable (such as BMI, blood pressure, and glycemic index), while classification models are used to predict a categorical variable (such as death, diagnosis, and hospital readmission).

Regression and classification problems have different performance measures. For the former, the predictive performance is frequently measured by the distance between the predicted and real value, by using, for example, the mean absolute error (MAE) or the square root of the mean squared error (RMSE). The RMSE has been more commonly used in epidemiological studies and is calculated by adding the square of the predicted errors, dividing by the number of observations, and then taking the square root to return to its original scale:

$$\mathrm{RMSE} = \sqrt{\frac{1}{n}\sum_{j=1}^{n}\left(y_j - \hat{y}_j\right)^2}$$

For predicting categorical variables, there are a few more options. The simplest is to analyze the accuracy, that is, the percentage of correct predictions. The problem with this measure is that in the case of rare outcomes, algorithms tend to predict non-occurrence of this event in all, or almost all, cases. Thus, the accuracy here would be high, but the predictive result would have little practical interest, because of its low generalization power for future samples.

One solution to this problem is to analyze both sensitivity and specificity, which are defined as:

$$\mathrm{Sensitivity} = \frac{\mathrm{True\ positives(prediction)}}{\mathrm{Positives(real)}}$$

$$\mathrm{Specificity} = \frac{\mathrm{True\ negatives(prediction)}}{\mathrm{Negatives(real)}}$$

The analysis of sensitivity and specificity helps to focus on both positive and negative predictions. The main issue here is the lack of a single value to directly compare the predictive performance of different outcomes and algorithms. The solution is to analyze the Receiver Operating Characteristic (ROC) curve, which plots the true positive rate (sensitivity) and the false positive rate (1 – specificity) at various classification thresholds.

The greatest technical challenge of machine learning is the presence of overfitting, which occurs when the algorithms work very well for the data in which they were trained but do not generalize well for future samples. This is common for complex predictive models that end up memorizing the data rather than identifying general patterns. The problem with memorizing information is that new data are always influenced by random factors and measurement errors, so it is important for models to learn general rules for decision-making rather than focusing too much on details.

There is, therefore, a trade-off in the development of predictive models in which we want models that perform well in the training data, but that are not so complex as to not generalize well for future samples. Thus, it is important to add regularizing hyperparameters to the algorithms that frequently aim to reduce their tendency to be very complex. Each algorithm has its possibilities of regularizers: for example, in the case of the random forests algorithm, one can control the total number of decision trees, the depth of these trees, and the number of variables considered in each node of the trees.

A historical goal of machine learning is the discovery of a master algorithm that is capable of making the best decisions in all areas and with all types of data [4]. However, it has not yet been possible to achieve the analytical flexibility needed for this and, especially in the case of structured data, it is still necessary to test the predictive performance of several algorithms to find out which one is best suited to a specific problem.

There are currently thousands of machine learning algorithms available, and it is not possible to determine a priori which algorithm will work best for each specific problem because of the "no-free-lunch theorem" (▶ Box 23.2). However, there are some algorithms that usually present better results in practice, especially in the case of the prediction of structured data, such as random forests, gradient boosted trees, and neural networks.

Box 23.2 The No-Free-Lunch Theorem

The No-Free-Lunch Theorem states that given an infinite possibility of distributions of data, there is no algorithm that will work best for every single problem. This means that it is important to test at least a few different algorithms for each specific problem. A recent study by Olson et al. (2018) [29] analyzed the predictive performance of 13 algorithms on 165 different data sets. The authors found an important variability regarding which algorithm performed best for each problem. For example, there were nine data sets for which multinomial naïve Bayes performed as well as or better than gradient boosted trees, despite them being the overall worst and best performing algorithms, respectively.

23.7 Machine Learning Algorithms

23.7.1 Random Forests

The random forests algorithm is composed of decision trees, which divide the variables sequentially in order to separate the observations into smaller and more homogeneous groups in relation to the outcome of interest. The random forests algorithm is therefore an ensemble of decision trees in which, for each independent tree, a bootstrap of the observations is performed and only some of the variables can be considered in each node of the tree. The final prediction is given by aggregating the results of all trees, which can be by the proportion of total votes (in the case of classification problems) or an average of the results (in the case of regression problems).

23.7.2 Gradient Boosted Trees

Gradient boosted trees is an algorithm that has gained recent popularity in machine learning mainly for its surprising results in data science competitions like Kaggle. As in the case of random forests, it is also an ensemble of decision trees, but in which the models are sequentially trained, each attempting to correct the former by adjusting the residuals from the previous tree.

23.7.3 Artificial Neural Networks

Artificial neural networks have been historically inspired by the functioning of the human brain. As in the case of human brains, signals are processed and transmitted sequentially until an output is reached. Artificial neural networks are composed of an input layer of predictive variables, a hidden layer composed of a few units (neurons) that transforms these inputs, and an outcome layer that gives the final prediction. In the case where more than one hidden layer is present, it is known as a deep neural network (deep leaning), an algorithm that has been responsible for most of the recent breakthroughs in machine learning.

23.8 Implementation of Big Data Acquisition, Storage, and Processing

Several methodological challenges exist with respect to using big data for dental research, and the following issues have already been described above:

- Big data are often not originally collected for research purposes (e.g., administrative data).
- Multiple errors can occur during data entry and processing (human and technical errors).
- Difficulties exist with unifying different classification systems (e.g., transition between various versions of ICD).
- Spurious correlations: large numbers of observations can result in statistically significant parameter estimates purely by chance.

In addition, acquiring and handling big data for dental research can be a logistically complex endeavor. Responsible data sharing often necessitates the establishment of a legally binding data usage agreement between the data owner and the data processor (usually the researcher). Thereby, all applicable rules and regulations with respect to warranting data privacy need to be addressed by means of appropriate data encryption, secure data storage/remote access, appropriate data-linkage approaches, adequate means of de-identification

(pseudonymization, anonymization), as well as making data available only when required but not otherwise (data lifecycle management). Note that the applicable norms, rules, and regulations for data projection are subject to change over time (see, e.g., the recent adoption of the General Data Protection Regulation (GDPR) in the EU).

Box 23.3 Process Model for Acquiring Routine Data for Health Services Research

***First stage*:** - Preparation of data access and usage: formal definition of general conditions.

***Second stage*:** - Sample data transfer: test the suitability of prerequisites and systems.

***Third stage*:** - Quality & validity audit: check sample data quality and compliance with regulations.

***Fourth stage*:** - Full-scale data access to exchange all data as contractually specified.

(source: Haux et al. [10])

Given the complexities of acquiring multi-country health insurance claims data for dental research purposes, a process model was recently developed in the context of the European Commission funded Horizon 2020 research project ADVOCATE. The model distinguishes between four stages (see ► Box 23.3) and provides a framework for standardized data acquisition.

Finally, the handling of large amounts of high-dimensional data often necessitates a suitably designed analytics platform such as a Data Warehouse. For data import and harmonization, the Integrating the Health Care Enterprise initiative (IHE – ► https://www.ihe.net/) promotes the coordinated use of established standards such as DICOM and HL7 FHIR. Data Warehouses often lean on informatics frameworks such as i2b2 or tranSMART. For example, the multi-institutional dental data repository BigMouth has adopted the i2b2 data warehousing platform and mapped data from each institution to a common reference terminology [27]. A Digital Research Environment (DRE) in the style of a Software as a Service platform may also provide an alternative for analytics. Note that the technical and logistical complexities involved in the handling of big data can imply considerable costs.

23.9 Conclusion

In this chapter, we have highlighted the opportunities and challenges of big data and machine learning in relation to oral epidemiology. This dynamically evolving and highly innovative field of research offers vast opportunities conducive to the creation of knowledge and (artificial) intelligence for the better promotion, protection, and management of people's oral health. Yet, in order to be useful, any type of big data analytics should be grounded in sound theoretical frameworks and guided by relevant clinical and population health questions.

References

1. Baâdoudi F, Duijster D, Maskrey N, Ali FM, Listl S, Whelton H, van der Heijden GJMG. Improving oral healthcare using academic detailing – design of the ADVOCATE Field Studies. Acta Odontol Scand. 2019;21:1–8.
2. Chalkley M, Listl S. First do no harm – the impact of financial incentives on dental X-rays. J Health Econ. 2018;58:1–9.
3. DeRouen TA. Promises and pitfalls in the use of "big data" for clinical research. J Dent Res. 2015;94(9 Suppl):107S–9S.
4. Domingos P. The master algorithm: how the quest for the ultimate learning machine will remake our world. New York: Basic Books; 2018.
5. Faiad Y, Khoury B, Daouk S, Maj M, Keeley J, Gureje O, Reed G. Frequency of use of the international classification of diseases ICD-10 diagnostic categories for mental and behavioural disorders across world regions. Epidemiol Psychiatr Sci. 2018;27(6):568–76.
6. Feres M, Louzoun Y, Haber S, Faveri M, Figueiredo LC, Levin L. Support vector machine-based differentiation between aggressive and chronic periodontitis using microbial profiles. Int Dent J. 2018;68(1):39–46.
7. Gartner. Gartner says solving ‚big data' challenge involves more than just managing volumes of data. 2011. http://www.gartner.com/newsroom/id/1731916.
8. Glick M. Taking a byte out of big data. J Am Dent Assoc. 2015;146(11):793–4. https://doi.org/10.1016/j.adaj.2015.09.002.
9. Glymour MM, Bibbins-Domingo K. The future of observational epidemiology: improving data and design to align with population health. Am J Epidemiol. 2019;188(5):836–9. https://doi.org/10.1093/aje/kwz030.
10. Haux C, Rosing K, Knaup P, Listl S, Kalmus O. A process model for acquiring international administrative routine data for health services research. GMS Med Inform Biom Epidemiol. 2019;15(1):Doc04. https://doi.org/10.3205/mibe000198.
11. Heo Y, Usama M, Yang J, Hossain MS, Ghoneim A. Recurrent convolutional neural network based multimodal disease risk prediction. Futur Gener Comput Syst. 2019;92:76–83.
12. Hujoel PP, Cunha-Cruz J, Kressin NR. Spurious associations in oral epidemiological research: the case of dental flossing and obesity. J Clin Periodontol. 2006;33(8):520–3.
13. Kalenderian E, Ramoni RB, White JM, Schoonheim-Klein ME, Stark PC, Kimmes NS, Patel VL, Walji MF. The importance of using diagnostic codes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(1):4–5; author reply 5. https://doi.org/10.1016/j.tripleo.2011.01.047.
14. Kalenderian E, Obadan-Udoh E, Yansane A, Kent K, Hebballi NB, Delattre V, Kookal KK, Tokede O, White J, Walji MF. Feasibility of electronic health record-based triggers in detecting dental adverse events. Appl Clin Inform. 2018;9(3):646–53.
15. Laney D. 3D data management: controlling data volume, velocity, and variety, application delivery strategies. Published by META Group Inc.; 2001.
16. Listl S, Jürges H, Watt RG. Causal inference from observational data. Community Dent Oral Epidemiol. 2016;44(5):409–15.

17. Matsuyama Y, Jürges H, Listl S. The causal effect of education on tooth loss: evidence from United Kingdom schooling reforms. Am J Epidemiol. 2019;188(1):87–95.
18. Munz M, Willenborg C, Richter GM, Jockel-Schneider Y, Graetz C, Staufenbiel I, et al. A genome-wide association study identifies nucleotide variants at SIGLEC5 and DEFA1A3 as risk loci for periodontitis. Hum Mol Genet. 2017;26(13): 2577–88.
19. Nakano Y, Suzuki N, Kuwata F. Predicting oral malodour based on the microbiota in saliva samples using a deep learning approach. BMC Oral Health. 2018;18(1):128.
20. Olshan AF, Diez Roux AV, Hatch M, Klebanoff MA. Epidemiology: back to the future. Am J Epidemiol. 2019;188(5):814–7.
21. Seitz MW, Haux C, Knaup P, Schubert I, Listl S. Approach towards an evidence-oriented knowledge and data acquisition for the optimization of interdisciplinary care in dentistry and general medicine. Stud Health Technol Inform. 2018;247:671–4.
22. Shetty V, Yamamoto J, Yale K. Re-architecting oral healthcare for the 21st century. J Dent. 2018;74(Suppl 1):S10–4.
23. Shungin D, Cornelis MC, Divaris K, Holtfreter B, Shaffer JR, Yu YH, et al. Using genetics to test the causal relationship of total adiposity and periodontitis: mendelian randomization analyses in the gene-lifestyle interactions and dental endpoints (GLIDE) consortium. Int J Epidemiol. 2015;44:638–50.
24. Srivastava M, Kumar P, Pradhan L, Varadarajan S. Detection of tooth caries in bitewing radiographs using deep learning. arXiv. 2017;1711:07312.
25. Xu K, Lam M, Pang J, Gao X, Band C, Mathur P, et al. Multimodal machine learning for automated ICD coding. aXiv. 2018;1810:13348.
26. Walji MF. Electronic health records and data quality. J Dent Educ. 2019;83(3):263–4.
27. Walji MF, Kalenderian E, Stark PC, White JM, Kookal KK, Phan D, Tran D, Bernstam EV, Ramoni R. BigMouth: a multi-institutional dental data repository. J Am Med Inform Assoc. 2014;21(6):1136–40.
28. Park WJ, Park JB. History and application of artificial neural networks in dentistry. Eur J Dent. 2018;12(4):594–601.
29. Olson RS, Cava W, Mustahsan Z, Varik A, Moore JH. Data-driven advice for applying machine learning to bioinformatics problems. Pac Symp Biocomput. 2018;23:192–203.

Epigenetics in Oral Health

Toby Hughes

Contents

24.1 Introduction – 368

24.2 Defining Epigenetics – 369

24.3 Epigenetic Molecular Mechanisms – 369
24.3.1 DNA Methylation – 370
24.3.2 Histone Modification – 370
24.3.3 DNA Methylation and Histone Acetylation Interaction – 370
24.3.4 Non-coding RNA – 370

24.4 Examples from Biology and Medicine – 371
24.4.1 Genetic Imprinting – 371
24.4.2 Cancer – 372
24.4.3 Environmental Stressors – 372
24.4.4 Behaviour – 372

24.5 Epigenetics in Oral Health – 372
24.5.1 Tooth Development – 373
24.5.2 Dental Caries – 373
24.5.3 Immunology and Periodontitis – 373
24.5.4 Oral Cancer – 374

24.6 Clinical Applications – 374
24.6.1 Personalised Medicine – The Potential of Epigenetics for Diagnosis and Therapy – 374
24.6.2 Epigenetic Modifications as Biomarkers of Exposure, Disease and Treatment Response – 375
24.6.3 Epigenetic Tools to Modify Gene Expression – 375
24.6.4 Epidrugs – 375
24.6.5 Other Fields of Research – 375

24.7 Conclusion – 375

References – 376

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_24

24

Learning Objectives

- To understand that epigenetic mechanisms are dynamic regulators of gene expression during normal development and facilitate adaptation to environmental stressors in individuals
- To develop a basic understanding of the three main epigenetic mechanisms: DNA methylation, histone acetylation, non-coding RNAs
- To appreciate that epigenetic changes are implicated in many complex diseases
- To explore how epigenetically modified molecules might act as early biomarkers of health and disease and to gain an appreciation for the potential use of epigenetic factors therapeutically

24.1 Introduction

At a population-level, long-term environmental change drives evolutionary adaptation in the genome, which, despite recent advances in gene-editing approaches, is not conducive to simple modification. At the level of the individual, however, short- and medium-term adaptation of the genome to environmental stressors is the domain of the *epigenetic architecture*, which dynamically regulates *gene expression* and function. This is particularly important for our understanding of oral health because epigenetic changes represent potential *biomarkers* of underlying health or disease in individuals. Furthermore, in many cases epigenetic changes are reversible, offering scope for intervention through *epigenetic modification*. Although there is now a substantial amount of published research on epigenetics in medicine and biology, epigenetics in oral health research is in its infancy. It promises, however, to become increasingly relevant to our understanding of the oral condition because of the role it plays in gene expression and, potentially, disease-susceptibility.

The human genome is composed of approximately 20,000 genes which encode information for approximately 200,000 different functional proteins, the building blocks and chemical catalysts of the body. All cells in the human body, (with a few notable exceptions) contain the same complement of genes, located in the nucleus (aside from the mitochondrial DNA) and arranged in long, linear chromosomes comprising 22 pairs of autosomes and 1 pair of sex chromosomes. As diploid organisms, each cell contains two gene copies, a paternally derived copy and a maternally derived copy (the exceptions being spermatozoa and oocytes). Unsurprisingly, not all genes are expressed at all times in all cells; there is a sophisticated molecular regulatory framework, the 'epigenome', of gene expression that is evident at multiple levels and is in situ even prior to fertilisation (e.g. *genetic imprinting* in the oocyte and spermatozoon).

The study of epigenetics is concerned with alterations in gene expression without an alteration in the DNA sequence itself. It has received increasing attention since the completion of the Human Genome Project in 2003, which revealed a lack of causal relationships between specific genes and complex disease [1]. This finding shifted the focus of researchers to identifying other factors in the development of disease. Primarily, this has involved exploring the interaction between genes and the environment: the field of epigenetics examines the molecular mechanisms that link the two. Epigenetic mechanisms have been implicated in many disease processes, including recent research that suggests epigenetics may also explain inter-generational disease susceptibility unexplained by variation in the genetic code itself [2], the concept of 'genetic memory'.

Two classes of information are encoded within the human genome, conferred by discrete chemical structures. The first, and most well-studied, class contains information encoded statically by four nitrogenous bases arranged in pairs in a double helix of deoxyribonucleic acid (*DNA*). The genetic code contains all the information required to produce proteins needed for growth, development and maintenance during an individual's life, but it does not contain the 'program' that determines when and where genes are expressed. The second class of information, contained in a series of dynamic chemical structures, dictates when and where various genes are activated and deactivated during embryogenesis, growth and throughout life. It is this epigenetic code that allows genetically identical cells to express different patterns of genes, resulting in distinct cell populations with different phenotypes and functions.

The epigenetic code works through chemical modifications that influence different aspects of the conformation of DNA, without altering the nucleotide code itself. This includes modifications of the linear structure of DNA (DNA *methylation*), as well as modifications of structural complexes around which DNA is packaged (*histone protein acetylation* in nucleosomes) and by elaboration of extra-genetic non-coding ribonucleic acids (nc*RNA*s). Many epigenetic modifications affect genetic expression by switching genes on or off and hence preventing messenger RNA (mRNA) formation or by affecting protein structure after translation from an mRNA template. In either case, the mechanism affects protein production and so affects genetic expression. These modifications can work in isolation, but tend to work in concert, especially methylation and histone-protein acetylation [3]. Epigenetic modifications change with time and are tissue specific, unlike the genetic code which usually does not change over time and is identical in 99% of the cells in the body. Epigenetic modifications have been shown to be responsible for our developmental program, turning genes on and off at precise moments during

embryonic development. Furthermore, some epigenetic modifications are stable and can be inherited from cell cycle to cell cycle and from parents (possibly even grandparents) to children [4–6].

Epigenetic modifications of the genetic code are caused by environmental stimuli and hence are responsible for our ability to adapt to different environments. This adaptation is not limited to physical adaptations alone but also influences behavioural and emotional responses to stress or trauma. Significant research is now focusing on epigenetics as a means to explain differences in *phenotype* that cannot be explained by conventional genetic approaches [1, 7, 8]. Epigenetic changes have been implicated in many disease states and pathologies, including cancers, inflammatory diseases, and autoimmune disorders [9, 10].

24.2 Defining Epigenetics

The term epigenetics was used first by Conrad Waddington in 1942, more than a decade before the structure of DNA was described by Watson and Crick in 1953 [11]. Waddington recognised that something must be acting on the genome in order to regulate it, coining the term '*epigenesis*' to describe organismal development; that is, the development of a complex being from a *totipotent* stem cell (Fig. 24.1). Implicit in this definition are the temporal and spatial components of epigenetics that modern research is only just describing, some half a century after Waddington [11–14].

Waddington's *epigenetic landscape* is a metaphor for how gene regulation modulates cellular development. Picture a ball rolling down a hill. The ball's trajectory will be influenced by variations in the landscape. These variations represent the underlying influence of the genes on cell fate, with perturbation in gene influence altering the cell's differential pathway. Grooves and ridges on the slope represent the increasing irreversibility of cellular differentiation. The ball will come to rest at the lowest possible point, representing the ultimate cell fate, or tissue type. This concept has been formalised in the context of a systems dynamics state approach to the study of cell-fate, which has opened the door to the key role played by stochastic fluctuation (cellular noise), as well as physical fields, in both cell differentiation and cell proliferation.

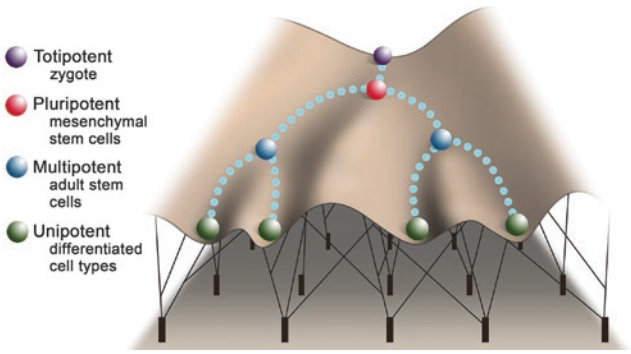


Fig. 24.1 Waddington's epigenetic landscape [15]

Modern molecular approaches are helping to provide a mechanistic framework for a functional epigenome, and clinical studies of individuals and populations are examining the role of the epigenome in health and disease. For the purposes of this chapter, a working definition of epigenetics will be a group of acquired or inherited (and potentially trans-generational), dynamic molecular mechanisms that are affected by the environment and act directly upon the genome and genetic machinery throughout life to regulate gene expression.

24.3 Epigenetic Molecular Mechanisms

Environmentally induced epigenetic regulation of gene activity occurs by one of two methods, either by affecting *chromatin condensation* (DNA methylation and histone protein modification) or by preventing protein production directly (non-coding RNA) [9, 16–19]. This section will discuss the general structure of the human genome to provide a context for later sections, which discuss the specifics of the different epigenetic modifications.

The 23 human chromosomes are comprised of varying continuous lengths of double-stranded linear DNA that are wrapped around structural proteins (histone proteins) and then further coiled and super-coiled. Stretched end to end, human DNA is 2 m long, but it is condensed into a nucleus that may only be 0.5 μm in diameter. Due to the condensation required for chromosomes to be packaged into a nucleus, the genes on a chromosome are normally inaccessible for transcription and ultimately protein production; local sections of the strand must be 'unwound' in order to provide access for transcription factors and the machinery required to commence transcription. The genetic material in the nucleus is variably packaged in different densities, reflecting the level of active transcription. The less densely packed material, *euchromatin*, is relatively uncondensed and allows for active transcription of the coding regions in the uncondensed areas. The more densely packed material, *heterochromatin*, is too condensed to allow transcription activating factors to bind to promoters on the strand to start transcription. Epigenetic mechanisms influence the level of chromatin condensation and therefore the amount of genetic transcription.

Epigenetic mechanisms have been found to affect both coding and non-coding regions of the genome. The *coding regions* account for 2% of the length of our DNA and contain approximately 20,000 genes [19] that, whose

mRNA products, when spliced during *post-translational modification*, can produce approximately 200,000 proteins. It was originally thought that the remaining non-coding regions contained only space-filling 'junk DNA'. Research has, however, shown that these regions are likely to be crucial for gene regulation and the structural integrity of the strand; they are fundamental for epigenetic modification [20, 21].

24.3.1 DNA Methylation

Each DNA strand is macromolecule composed of covalently bound repeating monomers called *nucleotides*. Each nucleotide contains a five-carbon sugar and a phosphate group (when arranged sequentially, these comprise the sugar-phosphate 'backbone' of DNA), and one of four nitrogenous bases: adenine (A), thymine (T), guanine (G), and cytosine (C). Specific nucleotides on one strand are always paired with those of the opposite strand, based on their nitrogenous base: A with T, and G with C. There are approximately equal numbers of each nucleotide in the whole genome. DNA methylation is a covalent modification of cytosine in the DNA. It occurs by the addition of a *methyl group* to a cytosine residue on the linear DNA strand; methylation only occurs, however, where cytosine is adjacent to guanine. It is important to differentiate between C being adjacent to G (in the case of a *CpG group*/dinucleotide) on the same strand, rather than opposite G (as in the case of C-G base pairing) on the opposing strand. This distinction is significant because adjacent Cs and Gs form a palindrome once complimentary base pairing occurs. This allows methyl groups to survive DNA replication and is fundamental for *methylome* stability; this is important for all models of trans-generational inheritance as it allows the genetic program to survive from one cell generation to the next [22].

CpGs are under-represented in the genome; they occur less frequently than chance predicts. Furthermore, CpGs tend to occur in clusters so that when they do occur, they are vastly over-represented in these areas. These clusters of CpGs are known as *CpG islands*, and they tend to occur in the promoter regions of genes [9]. CpGs also occur throughout the remainder of the genome, although significantly less frequently than in the CpG island regions, and less than chance suggests. Studies have shown that although these CpGs do not relate directly to a gene when compared with CpG islands in gene promoters, they are associated with many disease states [23, 24]. *Hyper-methylation* of CpG islands results in inhibition of gene transcription in the area, and *hypo-methylation* results in activation of these genes; variation in DNA methylation occurs at specific genes, but can also show a trend across the entire genome [24].

24.3.2 Histone Modification

Histone proteins form the core proteinaceous structure around which DNA is wrapped; the histone protein along with its associated part of the DNA strand form *nucleosomes*. The structure of the nucleosome determines how the DNA further condenses, and this ultimately affects gene expression. The most common form of histone modification is acetylation of its eight subunits, which are referred to as octamers [25].

Like hypo- and hyper-methylation, both hyper- and hypo-acetylation can affect chromatin condensation and allow or prevent gene transcription, respectively, although the mechanisms are different. Like DNA methylation, histone acetylation is also associated with both site-specific and genome-wide chromatin structure and therefore gene transcription. Histone acetylation is also associated with DNA synthesis and damage repair. Like methylation, histone modifications are heritable and survive DNA replication [26, 27].

24.3.3 DNA Methylation and Histone Acetylation Interaction

DNA methylation is a chemical modification of the DNA itself, whereas histone protein modifications are chemical modifications of one of the key proteins around which DNA wraps. Both exert a major influence on chromatin structure, and therefore gene expression. Despite both acting in different regions and using different enzymes, there is likely a reflexive relationship between these two systems. Indeed, recent research has demonstrated that the enzymes from the two systems may interact directly [3].

The interrelationship between DNA methylation and histone protein modification is particularly important for somatic cell reprogramming and stem cell research. During development, pluripotent stem cells lose their potency and eventually become terminally differentiated. This process is tightly regulated and involves a complex interplay between DNA methylation and histone protein modification. It is important because the process can be reversed so that somatic cells can be reprogrammed back to a pluripotent state [28]. Figure 24.2 illustrates the physical and chemical relationships between DNA and the two primary epigenetic mechanisms.

24.3.4 Non-coding RNA

RNA is the coding unit from which proteins are produced. DNA is transcribed into RNA and RNA is translated into protein. Unlike DNA, RNA is a single-

stranded. RNA contains the same nucleotides as DNA, aside from having uracil (U) instead of thymine (T). The similarity between the nucleotides in RNA and DNA allows them to share a complementary 'language'.

The two complementary strands of DNA in the double-helix are separated during transcription so that one of the strands of DNA can be transcribed to form a single strand of messenger RNA (mRNA). mRNA is one of several types of eukaryotic RNA. Broadly, RNA can be divided into coding and non-coding RNA. Coding RNAs possess an open *reading frame* and are translated to proteins, whereas non-coding RNAs (ncRNAs) do not possess an open reading frame and do not elaborate proteins; although they are themselves active.

It is estimated that only 2–5% of RNA codes for proteins, either structural or enzymatic. The remaining 95% of RNA is non-coding [29]. Non-coding RNAs are functionally relevant RNA molecules, despite not encoding for a protein. This group of RNAs includes a wide range of important RNAs such as transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), microRNAs (*miRNAs*) and short-interfering RNAs (*siRNAs*). The latter RNAs, miRNAs and siRNAs, which represent only a small proportion on the total ncRNAs, have been shown to regulate gene expression epigenetically. For instance, miRNAs are small single-stranded non-coding RNAs (20–24 nucleotides) that negatively regulate the expression of their target genes at the post-transcriptional level [30, 31]. miRNAs bind to the 3′ untranslated region (3′UTR) of their target messenger RNAs (mRNAs) and lead to subsequent degradation or translational repression of the bound mRNA through recruitment of the RNA-induced silencing complex [29]. Guo and colleagues suggested that reduction of the protein level by endogenous miRNAs is caused by destabilisation of the target mRNA [32]. Recent studies have reported that miRNAs are involved in multiple vital processes, throughout the regulation of development or differentiation of a disease [30–32].

More recent analysis of the data from the human genome project has shown that although the number of protein coding genes in the human genome has remained largely unchanged, there could be around 20,000 'dead genes' hidden in the genome. It is thought that these genes do not code protein, but that the RNA generated by them exerts significant effects on the expression of protein-coding genes [33].

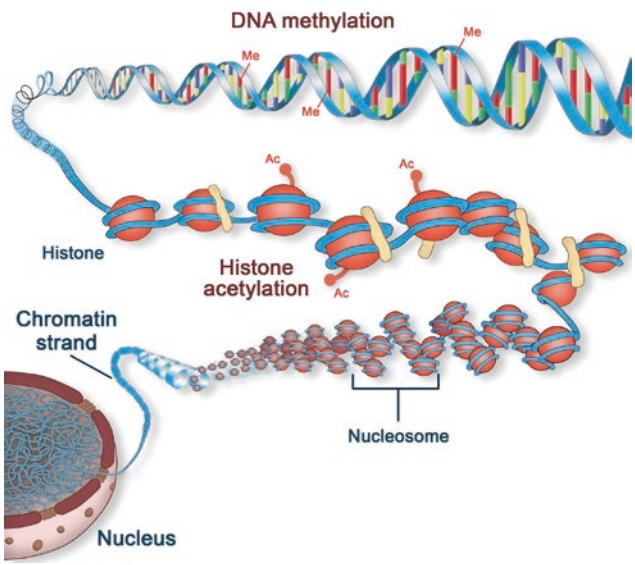


Fig. 24.2 Epigenetic regulation of DNA transcription within a specific cell or tissue acts at two levels of DNA organisation: by control of histone acetylation regulating enzymatic access and by methylation of specific cytosine nucleic acids in the DNA regulating mRNA transcription; further epigenetic regulation by microRNA action on messenger RNA occurs post-transcriptionally [15]

24.4 Examples from Biology and Medicine

24.4.1 Genetic Imprinting

Usually both gene copies can be transcribed to produce proteins. Genetic imprinting is a phenomenon in which either the paternally or the maternally inherited gene copy is inactivated, and the other copy is transcribed. This means that for some genes to be active, they must be inherited from a specific parent. Imprinted genes therefore act very differently to non-imprinted genes. DNA methylation profiles can survive mitosis and have been implicated as the molecular control behind the process in which imprinted genes are faithfully reproduced in all daughter cells. It is thought that about 100 out of our 20,000 genes are imprinted. This number is probably conservative, with more imprinted genes being discovered, and even with such a small number, their effects can be profound [34–36].

Silencing of genes via imprinting has been found to have significant phenotypic effects. Prader-Willi and Angelman syndromes were the first disorders discovered to be associated with imprinting. Both are associated with the loss of a specific chromosomal region on chromosome 15 from one parent and silencing of the other copy due to sex-specific imprinting. If the loss of this chromosomal region is paternally inherited, then Prader-Willi syndrome results because of the silencing of the maternally derived SNRPN and necdin genes, along with clusters of genes coding for a series of small nucleolar RNAs. Patients with Prader-Willi syndrome usually display short stature, cognitive and behavioural problems, and chronic hunger that often leads to obesity. If the loss of the chromosomal region is maternally inherited, then Angelman syndrome will result as a consequence of the silencing of the paternally derived

SNRPN gene. Patients with Angelman syndrome show severe cognitive impairment, happy excitable demeanour and profound speech impairment.

24.4.2 Cancer

Most early epigenetics research focussed on cancer due to the known roles of methylation and acetylation in normal cell-cycle regulation, and putative mechanisms for dysregulation. In general, cancers present with genome-wide global hypo-methylation and gene-specific hyper-methylation. The hyper-methylation usually occurs within the promoters of tumour-suppressor genes, and this switches them off (silences them). Histone hypo-acetylation is also implicated in the silencing of tumour-suppressor genes. The absence of tumour-suppressor genes allows for the uncontrolled growth of cells and hence tumourigenesis. Tumours (malignant or benign) appear in the body regularly, but they are normally detected and eliminated quickly. Silencing of tumour-suppressor genes can have drastic implications for this process, especially when combined with overall hypo-methylation, which results in increased gene expression and therefore cell growth. This relationship has been demonstrated in many cancers, including oral squamous cell carcinomas (OSCCs) [37, 38].

24.4.3 Environmental Stressors

It is known that certain environmental stressors can induce changes in the human body. Epigenetics, particularly methylation, has been shown to provide this link between the environment and phenotype in many cases. For example, intrauterine nutrition can cause epigenetic changes via DNA methylation in the foetus. The effects of these changes can be immediately apparent, and some changes can persist and render their effects later in life. Foetal folate deficiency is one such example. If the mother does not consume enough dietary folate, there is a lack of methyl groups available for the epigenetic machinery. As a result, certain genes do not become methylated. This also results in chromosomal instability. Both epigenetic changes can cause birth defects, especially of the neural tube, and are associated with such problems as spina bifida [39, 40].

Exposure to environmental toxins in occupational chemicals, cigarette smoke, contaminated air and drinking water, as well as fossil fuel emissions, may cause epigenetic changes. For example, smoking has a measurable effect on DNA methylation and has been associated with hyper-methylation of tumour-suppressor genes [41–43]. Research has also shown that the variability in susceptibility to environmental and dietary toxins between people may be due to differences in how different individuals metabolise and process methyl groups generally. Differences in *methyl metabolism* may result in susceptibility to epigenetic changes that cause health problems.

24.4.4 Behaviour

Experiments in rodents have shown a strong link between adversity in early life and epigenetic profile in later life. It is hard to test this in humans as the brain is not accessible for testing in live subjects. However, studies of suicide victims have shown that those who were abused in early childhood had significantly higher levels of hyper-methylation of rRNA genes in neurones and, therefore, produced fewer ribosomes for protein production. Importantly, these changes were specific to the hippocampus, the part of the brain associated with memory formation [44–46].

24.5 Epigenetics in Oral Health

Although in its infancy, research into the role of the epigenome in oral health is expanding rapidly. Unsurprisingly, epigenetic factors have been implicated in various oral cancers, but there is mounting evidence of their role in growth disorders (cleft lip and palate and various oral-associated syndromes), odontogenesis, inflammatory disorders (gingivitis, periodontitis and other oral-systemic conditions), and even dental caries.

Changes of DNA methylation patterns and cytokine gene expression can be observed in chronic periodontitis [47–50]. In addition, methylation patterns may be different between healthy and inflamed dental pulp [51]. Recent studies have reported that histone modifications may induce differentiation and mineralisation in dental pulp stem cells [52–54]. Histone acetylation and deacetylation plays a crucial role in regulation of gene expression and may promote pulp repair and regeneration [52–56]. Other studies have reported that non-coding RNAs are involved in oral diseases such as specific syndromes, oral cancer and oral immunology [57, 58]. In addition, recent studies have demonstrated that miRNAs play essential roles in odontoblast differentiation [57, 58].

Overview

- Tooth development
- Dental caries
- Immunology and periodontitis
- Oral cancer

24.5.1 Tooth Development

Brook has described how dental development is a multi-level process, involving molecular and cellular interactions that lead to macroscopic outcomes [59]. Dental development is also a multi-dimensional process, involving changes in size and shape of developing tooth germs that occur in all three dimensions, with the fourth dimension of time superimposed. A series of reiterative signalling events occurs during odontogenesis, involving interactions between the oral ectodermal and neural crest-derived ectomesenchymal tissues. This series of interactions involves multiple genetic signalling pathways that are themselves influenced epigenetically by various extracellular factors. As Brook [59] has noted: 'Interactions, gradients and spatial field effects of multiple genes, epigenetic and environmental factors all influence the development of individual teeth, groups of teeth and the dentition as a whole'.

Over 300 genes have been identified as being involved in odontogenesis, with many of them playing a role in cellular communication [60]. Some of the genetic signalling pathways involved in this communication include Fgf, Bmp, Fgf, Shh, Wnt and Tnf. The reciprocal interactions between the ectodermal and ectomesenchymal tissues regulate key stages in the process of odontogenesis, including initiation, morphogenesis and differentiation.

Evidence of epigenetic factors playing an important role in normal tooth development come from several sources. For instance, histone demethylase may regulate dental stem cell differentiation [59]. In addition, histone acetyltransferase and non-coding RNAs may influence odontogenic differentiation [56, 57].

A review paper by Townsend and colleagues examined the role of the epigenome in tooth development, and specifically a putative role in agenesis and supernumerary teeth [61]. The authors noted that studies of monozygotic twin pairs reared together, who display discordances in the number of missing or extra teeth provide support for the role of epigenetic influences on dental development [62, 63]. The reviewed literature supported the view that supernumerary tooth formation is influenced not only by genetic factors but also by environmental and epigenetic influences. Hughes provided evidence of differentially methylated regions associated with supernumerary teeth in a small cohort of monozygotic twin children [64]. Gene ontology analysis revealed that many of the regions were at or near genes associated with inter-cellular communication, a key component of the reciprocal induction that occurs during odontogenesis.

24.5.2 Dental Caries

Caries is a multifactorial disease. Host genome contributions to variation in caries liability have been widely reported [65, 66], with estimates ranging from 30% to 70%. Specific genes that have a demonstrated association with caries include those associated with taste preference and saliva composition [67, 68]. To-date, however, most genome-wide association studies have failed to explain a large proportion of the observed genetic variance even after adjusting for known environmental covariates – a case of 'missing' heritability. Could this be a case of heterogeneous expression because of background epigenetic variability? Recent analysis of data from a cohort of monozygotic twins discordant for dental caries suggests that, at least at a genome-wide level, discordance may be correlated with methylation profile (Author, unpublished). Another ongoing study of mother-child dyads has developed a protocol for assessing maternal, environmental and epigenetic risk factors for dental caries in children with the aim. Early pilot data are also suggestive of an epigenetic influence on early childhood caries risk [69].

24.5.3 Immunology and Periodontitis

Across any given population, people will display varied inflammatory and immune responses to a given stimulus. Research has shown that much of the variability is due to differences in what is a highly complex polygenic immune system; however, more recent research is demonstrating that the immune system and inflammatory responses are highly dependent upon epigenetic mechanisms to function. This has implications for all inflammatory diseases, including periodontitis [70].

Cytokines are some of the biomolecules constituting the inflammatory response. These substances are small proteins that act as chemical messengers and modulate the immune response. Broadly, there are pro-inflammatory cytokines and anti-inflammatory cytokines. The balance of these cytokines determines what response is taken by the immune system to environmental stimuli. In the case of periodontitis in a susceptible host, toxins and breakdown products from bacteria and immune cells result in a significant predisposition towards a pro-inflammatory cytokine response to these stimuli, causing the development of a hyper-inflammatory response with concomitant periodontal breakdown.

It is now evident that epigenetic changes in the genes encoding cytokines can alter their expression, leading to either pro- or anti-inflammatory responses. Studies have shown that epigenetic changes of the genes encod-

ing pro-inflammatory cytokines are associated with periodontitis [49]. Other studies have shown an association between epigenetic changes and periodontitis [50, 71, 72]. Most published studies have focused on chronic periodontitis; a link, however, has also been established between DNA methylation of pro-inflammatory mediator genes and aggressive periodontitis [73].

One of the most revealing studies has shown a link between periodontitis and HIV-1 and AIDS progression [74]. Specifically, it was shown that periodontitis can reactivate HIV-1 expression through an epigenetic mediator. This study not only shows a correlation between a systemic disease and periodontitis but also explains at least part of the molecular mechanism linking the two. The study goes further to suggest possible future treatment options that have already received FDA approval in the United States (for treatment of other conditions). The article mentions two 'epigenetic therapies' approved; one involves using suberoylanilide hydroxamic acid in the treatment of T-cell lymphomas, the other involves using DNA methyl transferase DNMT inhibitors for the treatment of myelodysplastic syndrome and leukaemia. Unfortunately, these treatments are associated with significant systemic effects, and no targeted epigenetic therapies have been developed to date. Nevertheless, this research suggests that targeted therapies could play a part in the management of HIV-AIDS and, possibly, periodontitis in the future.

The epigenetic changes on pro-inflammatory mediators in periodontal disease have been linked to several environmental stimuli, including smoking and nutrition, and the oral bacteria themselves. Iacopino states that these changes in the host tissues can facilitate bacterial colonisation, increase inflammatory damage and provide bacteria with increased levels of carbohydrate for metabolism [75]. The author also notes that these findings have implications for the methods used to diagnose periodontal disease and to identify patients at risk. He suggests that a new approach to management of periodontal problems in the future, based on personalised medicine, is likely to consider additional factors apart from bleeding and pocket depths, including types of bacteria present in the biofilm and epigenetic changes in the periodontal tissues [75].

24.5.4 Oral Cancer

Evidence is emerging that OSCCs accumulate epigenetic alterations, predominantly changes in methylation pattern. OSCC is a neoplastic form of cancer influenced by endogenous and environmental factors, including tobacco and alcohol exposure [76]. Interestingly, epigenetic factors may provide a putative link between inflammation and cancer [77]. Chronic inflammation induced by IL-6 may lead to hyper-methylation of tumour-suppressor genes, and hence contribute to the development of OSCC [78]. Aberrant methylation might also be triggered by inflammation caused by a specific population of oral pathogens, linking microflora, inflammation and tumorigenesis [79].

Pre-malignant lesions in the oral cavity include oral leucoplakia and oral lichen planus (OLP). Oral leucoplakia does in some cases develop into OSCC, but so far, the mechanisms for this transformation are still unknown and finding early markers is important for an early identification of patients at risk for developing OSCC [80]. An aberrant methylation pattern, similar to OSCC for certain genes, has been reported in oral leucoplakia, indicating that this epigenetic pattern may be linked to malignant transformation [80, 81]. Oral lichen planus is characterised by chronic inflammation in the oral mucosa [81]. Like leucoplakia, the exact aetiological mechanisms remain poorly understood. A correlation between increase in an acetylation of histone H3 and poor response to therapy of clinically severe lesions has been reported [82].

The role micro RNAs (miRNAs) in oral cancer has been extensively researched recently. miRNAs play a key role in tumourigenesis of cancer stem cells through mechanisms such as drug resistance, tumourigenicity and self-renewal [83]. Genome-wide studies have revealed some micro RNAs undergoing up-regulation and down-regulation in oral cancer lesions. In a meta-analysis, D'Souza and colleagues reported both over-expression and under-expression of various micro RNAs in up to 70% of OSCC lesions [84, 85]. miR-146a, miR-211, miR-31, miR-21, miR-204, miR-24 and miR155 were the most frequently over-expressed. Upregulation of these miRNAs was associated with clinico-pathological features like regional metastasis and advanced tumour stage [84–86].

24.6 Clinical Applications

24.6.1 Personalised Medicine – The Potential of Epigenetics for Diagnosis and Therapy

Clinical research has revealed that there is variation in the response to treatment among individuals, and specific therapies may be more or less effective in certain individuals. This variation in response to treatment has led to the concept of personalised medicine, using molecular analysis to tailor treatments to individuals based on their molecular profile. The characteristics of a patient can be grouped into genetic, epigenetic, proteomic, metabolomic and exposome categories. Knowledge of

epigenetics contributes to a better understanding of the interactions between genes and the environment and may provide explanations as to why patients with the same clinical phenotype respond differently to treatment [87].

24.6.2 Epigenetic Modifications as Biomarkers of Exposure, Disease and Treatment Response

As a dynamic expression of environmental exposure and/or disease progression, epigenetic alterations offer a new source of potential biomarkers for clinical application, both diagnostically and to monitor treatment response.

In addition, the possible use for buccal swabs, scraping of the oral mucosa or saliva for epigenetic analysis makes it clinically feasible as a diagnostic tool [80].

For periodontitis, which is a site-specific disease and differs in patient susceptibility to disease, identifying epigenetic markers may present biomarkers for identifying patients at risk of developing periodontitis

In OSCC, DNA methylation pattern changes occur during all stages of tumorigenesis from pre-malignancy to oral cancer. A recent review indicated that aberrant methylation could be an early indicator of disease development and progression in OSCC [88]. One putative marker, p16, was found to have an increase in hyper-methylation in dysplastic lesions compared to non-dysplastic lesions. In addition, a higher methylation was found in those dysplastic lesions that subsequently became malignant.

Regarding biomarkers for treatment response, known genetic variants of MGMT and MLH1 gene are strong predictors of response to chemotherapy in various cancerous lesion. These would form logical targets for investigation of the role of epigenetic mechanisms in personalised chemotherapy [89].

24.6.3 Epigenetic Tools to Modify Gene Expression

Until the recent advent of CRISPR/Cas9 gene editing approaches, pragmatic approaches to genetic modification had failed to deliver on the early promise from the wealth of information delivered by the Human Genome Project. Furthermore, even in the era of CRISPR, there are still significant hurdles, both technologically and ethically, limiting the utility of altering the nucleic acid code itself. Epigenetic mechanisms offer significant advantages in both areas. By their very nature, they are generally transient, reversible and tissue-specific, and hence lend themselves to time-limited, anatomically localised interventions that do not carry a significant risk of transmission into the germline. Potential applications in oral health include targeted therapies for specific oral cancers, and hard-tissue regeneration/remodelling. Early developmental disorders may also be a possible target, provided a suitable means of delivering the appropriate stimulus prenatally can be found.

24.6.4 Epidrugs

The fact that epigenetic mechanisms are reversible makes them attractive targets for new treatment models in both cancer and inflammatory diseases. The term '*epidrugs*' was coined by Ivanov and colleagues as 'drugs that inhibit or activate disease-associated epigenetic proteins ameliorating, curing or preventing the disease' [90]. In the field of cancer, there are numerous studies on the use of epidrugs as treatment models; at present, however, there is a lack of research on this in relation to oral health. Reports are emerging on the use of epidrugs in inflammatory diseases. It has been found that HDAC inhibitors suppress bone loss in rheumatoid arthritis as well as in periodontitis, and they have been suggested as potential treatment models for these diseases [91, 92]. Another clinical application for epigenetics is in tissue engineering, in which epidrugs have been suggested as a tool for modulating cell differentiation, thereby improving regeneration of tissue [93].

24.6.5 Other Fields of Research

This chapter has only briefly touched on some areas of oral health in which epigenetic research is currently underway; other areas showing significant promise include the regulation of early craniofacial embryogenesis; the role of epigenomic factors in orally involved syndromes; their role in oral clefting; and how they might be utilised to accelerate stem cell therapies for tissue repair.

24.7 Conclusion

Epigenetic mechanisms are responsible for the differential expression of genes across temporal and spatial fields, providing a mechanism for the regulation and control of normal growth and development, as well as the capacity to adapt dynamically to environmental stress. Implicated in many complex diseases, both systemically and orally, the study of the mechanisms underpinning these modifications is proving to be a valuable and insightful arm of genomics research. Ultimately, an

understanding of functional epigenetics is likely to yield significant further insight into the prevention, screening, diagnosis, prognosis and management of complex oral health conditions.

References

1. Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, et al. Missing heritability and strategies for finding the underlying causes of complex disease. Nat Rev Genet. 2010;11:446–50.
2. Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. Nature. 2007;447:433–40.
3. Cedar H, Yehudit B. Linking DNA methylation and histone modification: patterns and paradigms. Nat Rev Genet. 2009;10:295–304.
4. Kadauke S. Tissue specific epigenetic bookmarking to preserve transcriptional programs through mitosis. Dissertation, University of Pennsylvania, 2012.
5. Wilson AG. Epigenetic regulation of gene expression in the inflammatory response and relevance to common diseases. J Periodontol. 2008;79:1514–9.
6. Grossniklaus U, Kelly B, Ferguson-Smith AC, Pembrey M, Lindquist S. Transgenerational epigenetic inheritance: how important is it? Nat Rev Genet. 2013;14:228–35.
7. Slatkin M. Epigenetic inheritance and the missing heritability problem. Genetics. 2009;182:845–50.
8. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461:747–53.
9. Barros SP, Offenbacher S. Epigenetics: connecting environment and genotype to phenotype and disease. J Dent Res. 2009;88:400–8.
10. Khan SN, Khan AU. Role of histone acetylation in cell physiology and diseases: an update. Clin Chim Acta. 2010;411:1401–11.
11. Waddington C. Canalization of development and the inheritance of acquired characters. Nature. 1942;3811:563–5.
12. Van Speybroeck L. From epigenesiss to epigenetics: the case of C.H. Waddington. Ann N Y Acad Sci. 2002;981:61–81.
13. Haig D. The (dual) origin of epigenetics. Cold Spring Harbor Symposia on Quantitative Biology. 2004. Cold Spring Harbor Laboratory Press.
14. Holliday R. Epigenetics comes of age in the twenty first century. J Genet. 2002;81:1–4.
15. Williams SD, Hughes TE, Adler CJ, Brook AH, Townsend GC. Epigenetics: a new frontier in dentistry. Aust Dent J. 2014;59S:1–11.
16. Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. Nature. 2007;447:425–32.
17. Miska EA. How microRNAs control cell division, differentiation and death. Curr Opin Genet Dev. 2005;15:563–8.
18. Razin A, Kantor B. DNA methylation in epigenetic control of gene expression. Prog Mol Subcell Biol. 2005;38:151–67.
19. Meissner A. Epigenetic modifications in pluripotent and differentiated cells. Nat Biotechnol. 2010;28:1079–88.
20. Pennisi E. ENCODE project writes eulogy for junk DNA. Science. 2012;337:1159–61.
21. Biemont C. A brief history of the status of transposable elements: from junk DNA to major players in evolution. Genetics. 2012;186:1085–93.
22. Szyf M. Early life environment, DNA methylation and behavior. In: Craig JM, Wong NC, editors. Epigenetics: a reference manual. Norfolk, UK: Caister Academic Press; 2011. p. 3–24.
23. Deaton AM, Bird A. CpG islands and the regulation of transcription. Genes Dev. 2011;25:1010–22.
24. Sandoval J, Heyn H, Moran S, et al. Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. Epigenetics. 2011;6:692–702.
25. Voss AK, Thomas T. Concepts in histone acetyltransferase biology. In: Craig JM, Wong NC, editors. Epigenetics: a reference manual. Norfolk, UK: Caister Academic Press; 2011. p. 25–50.
26. Fraser P, Bickmore W. Nuclear organization of the genome and the potential for gene regulation. Nature. 2007;447:413–7.
27. Margueron R, Reinberg D. Chromatin structure and the inheritance of epigenetic information. Nat Rev Genet. 2010;11:285–96.
28. Cui HC. The epigenetic basis of cell fate specification and reprogramming. In: Craig JM, Wong NC, editors. Epigenetics: a reference manual. Norfolk, UK: Caister Academic Press; 2011. p. 183–94.
29. Saxena A, Carninci P. Non-coding RNA: an overview. In: Craig JM, Wong NC, editors. Epigenetics: a reference manual. Norfolk, UK: Caister Academic Press; 2011. p. 271–90.
30. Bayarsaihan D. Epigenetic mechanisms in inflammation. J Dent Res. 2011;90:9–17.
31. Kaikkonen MU, Lam MT, Glass CK. Non-coding RNAs as regulators of gene expression and epigenetics. Cardiovasc Res. 2011;90:430–40.
32. Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature. 2010;66:835–40.
33. Wellcome Trust Sanger Institute. Human genome far more active than thought. England: Wellcome Trust Sanger Institute; 2012. https://www.sanger.ac.uk/news/view/2012-09-05-human-genome-far-more-active-than-thought. Accessed 19 June 2019.
34. Ferguson-Smith AC. Genomic imprinting: the emergence of an epigenetic paradigm. Nat Rev Genet. 2011;2:565–75.
35. Barlow DP. Genomic imprinting: a mammalian epigenetic discovery model. Annu Rev Genet. 2011;45:379–403.
36. Sasaki H, Matsui Y. Epigenetic events in mammalian germ-cell development: reprogramming and beyond. Nat Rev Genet. 2008;9:129–40.
37. Feinberg AP, Tycko B. The history of cancer epigenetics. Nat Rev Cancer. 2004;4:143–53.
38. Sandoval J, Asteller M. Cancer epigenomics: beyond genomics. Curr Opin Genet Dev. 2012;22:50–5.
39. Meethal SV, Hogan KJ, Mayanil CS, Iskandar BJ. Folate and epigenetic mechanisms in neural tube development and defects. Childs Nerv Syst. 2013;29:1427–33.
40. Farkas SA, Böttiger AK, Isaksson HS, Finnell RH, Ren A, Nilsson TK. Epigenetic alterations in folate transport genes in placental tissue from fetuses with neural tube defects and in leukocytes from subjects with hyperhomocysteinemia. Epigenetics. 2013;8:303–16.
41. Lund G, Zaina S. Atherosclerosis: an epigenetic balancing act that goes wrong. Curr Atheroscler Rep. 2011;13:208–14.
42. Lund G, Zaina S. Atherosclerosis, lipids, inflammation and epigenetics. Curr Opin Lipidol. 2007;18:699–701.
43. Risch A, Plass C. Lung cancer epigenetics and genetics. Int J Cancer. 2008;123:1–7.
44. Lucassen PJ, Naninck EFG, van Gougoever JB, Fitzsimmons C, Joels M, Korosi A. Perinatal programming of adult hippocampal structure and function: emerging roles of stress, nutrition, and epigenetics. Trends Neurosci. 2013;36:621–31.
45. El-Sayed AM, Haloossim MR, Galea S, Koenen KC. Epigenetic modifications associated with suicide and common mood and anxiety disorders: a systematic review of the literature. Biol Mood Anxiety Disord. 2012;2:2–14.
46. Lang B, Alrahbeni TMA, St Clair D, Blackwood DH, McCaig CD, Shen S. HDAC9 is implicated in schizophrenia and

expressed specifically in post-mitotic neurons but not in adult neural stem cells. Am J Stem Cells. 2012;1:31–41.
47. Lindroth AM, Park YJ. Epigenetic biomarkers: a step forward for understanding periodontitis. J Periodontal Implant Sci. 2013;43:111–20.
48. Zhang S, Crivello A, Offenbacher S, Moretti A, Paquette DW, Barros SP. Interferon-gamma promoter hypomethylation and increased expression in chronic periodontitis. J Clin Periodontol. 2010;37:953–61.
49. Zhang S, Barros SP, Moretti AJ, Yu N, Zhou J, Preisser JS, et al. Epigenetic regulation of TNFA expression in periodontal disease. J Periodontol. 2013;84:1606–16.
50. Zhang S, Barros SP, Niculescu MD, Moretti AJ, Preisser JS, Offenbacher S. Alteration of PTGS2 promoter methylation in chronic periodontitis. J Dent Res. 2010;89:133–237.
51. Cardoso FP, Viana MB, Sobrinho AP, Diniz MG, Brito JA, Gomes CC, et al. Methylation pattern of the IFN-gamma gene in human dental pulp. J Endod. 2010;36:642–6.
52. Duncan HF, Smith AJ, Fleming GJ, Cooper PR. Histone deacetylase inhibitors induced differentiation and accelerated mineralization of pulp-derived cells. J Endod. 2012;38:339–45.
53. Duncan HF, Smith AJ, Fleming GJ, Cooper PR. Histone deacetylase inhibitors epigenetically promote reparative events in primary dental pulp cells. Exp Cell Res. 2013;319:1534–43.
54. Duncan HF, Smith AJ, Fleming GJ, Cooper PR. HDACi: cellular effects, opportunities for restorative dentistry. J Dent Res. 2011;90:1377–88.
55. Paino F, La Noce M, Tirino V, Naddeo P, Desiderio V, Pirozzi G, et al. Histone deacetylase inhibition with valproic acid downregulates osteocalcin gene expression in human dental pulp stem cells and osteoblasts: evidence for HDAC2 involvement. Stem Cells. 2014;32:279–89.
56. Wang T, Liu H, Ning Y, Xu Q. The histone acetyltransferase p300 regulates the expression of pluripotency factors and odontogenic differentiation of human dental pulp cells. PLoS One. 2014;9(7):e102117.
57. Sun Q, Liu H, Chen Z. The fine tuning role of microRNA-RNA interaction in odontoblast differentiation and disease. Oral Dis. 2014. https://doi.org/10.1111/odi.12237.
58. Perez P, Jang SI, Alevizos I. Emerging landscape of non-coding RNAs in oral health and disease. Oral Dis. 2014;20:226–35.
59. Brook AH. Multilevel complex interactions between genetic, epigenetic and environmental factors in the aetiology of anomalies of dental development. Arch Oral Biol. 2009;54S:S3–17.
60. Thesleff I. The genetic basis of tooth development and dental defects. Am J Med Genet. 2006;140A:2530–5.
61. Townsend GC, Bockmann MR, Hughes TE, Brook AH. Genetic, environmental and epigenetic influences on variation in human tooth number, size and shape. Odontology. 2012;100:1–9.
62. Townsend G, Hughes T, Luciano M, Brook A. Genetic and environmental influences on human dental variation: limitations and advantages of studies involving twins. Arch Oral Biol. 2009;54:S45–51.
63. Townsend G, Hughes T, Bockmann M, Smith R, Brook A. How studies of twins can inform our understanding of dental morphology. In: Koppe T, Meyer G, Alt KW, editors. Comparative dental morphology. Frontiers of oral biology, vol. 13. Basel: Karger; 2009. p. 136–41.
64. Hughes TE. The role of epigenetic factors in craniofacial development. J Dent Res. 2018;97B:0421.
65. Bretz WA, Corby PM, Hart TC, Costa S, Coelho MQ, Weyant RJ, et al. Dental caries and microbial acid production in twins. Caries Res. 2005;39:168–72.
66. Kuppan A, Rodrigues S, Samuel V, Ramakrishnan M, Halawany HS, Abraham NB, et al. Prevalence and heritability of early childhood caries among monozygotic and dizygotic twins. Twin Res Hum Genet. 2017;20:43–52.
67. Schaffer JR, Feingold E, Wang X, Lee M, TCuenco K, Weeks DE, et al. GWAS of dental caries patterns in the permanent dentition. J Dent Res. 2013;92:38–44.
68. Wendell S, Wang X, Brown M, Cooper ME, DeSensi RS, Weyant RJ, et al. Taste genes associated with dental caries. J Dent Res. 2010;89:1198–202.
69. Fernando S, Speicher DJ, Bakr MM, Benton MC, Lea RA, Scuffham PA, et al. Protocol for assessing maternal, environmental and epigenetic risk factors for dental caries in children. BMC Oral Health. 2015;15:167.
70. Martino DJ, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. Allergy. 2010;65:7–15.
71. Ohi T, Uehara Y, Takatsu M, Watanabe M, Ono T. Hypermethylation of CpGs in the promoter of the COL1A1 gene in the aged periodontal ligament. J Dent Res. 2006;85:245–50.
72. Nahid MA, Rivera M, Lucas A, Chan EK, Kesavalu L. Polymicrobial infection with periodontal pathogens specifically enhances microRNA miR-146a in ApoE-/- mice during experimental periodontal disease. Infect Immun. 2011;79:1597–605.
73. Andia DC, de Oliveira NF, Casarin RC, Casati MZ, Line SR, de Souza AP. DNA methylation status of the IL8 gene promoter in aggressive periodontitis. J Periodontol. 2010;81:1336–41.
74. Imai K, Ochiai K. Role of histone modification on transcriptional regulation and HIV-1 gene expression: possible mechanisms of periodontal diseases in AIDS progression. J Oral Sci. 2011;53:1–13.
75. Iacopino AM. Epigenetics: new explanations for old problems? J Can Dent Assoc. 2010;76:a76.
76. González-Ramírez I, Soto-Reyes E, Sánchez-Pérez Y, Herrera LA, García-Cuellar C. Histones and long non-coding RNAs: the new insights of epigenetic deregulation involved in oral cancer. Oral Oncol. 2014;50:691–5.
77. Kundu JK, Surh Y. Inflammation: gearing the journey to cancer. Mutat Res. 2008;659:15–30.
78. Gasche JA, Hoffmann J, Boland CR, Goel A. Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells. Int J Cancer. 2011;129:1053–63.
79. Bebek G, Bennett KL, Funchain P, Campbell R, Seth R, Scharpf J, et al. Microbiomic subprofiles and MDR1 promoter methylation in head and neck squamous cell carcinoma. Hum Mol Genet. 2012;21:1557–65.
80. Abe M, Yamashita S, Mori Y, Abe T, Saijo H, Hoshi K, et al. High-risk oral leukoplakia is associated with aberrant promoter methylation of multiple genes. BMC Cancer. 2016;16:350.
81. Asokan GS, Jeelani S, Gnanasundaram N. Promoter hypermethylation profile of tumor suppressor genes in oral leukoplakia and oral squamous cell carcinoma. J Clin Diagn Res. 2014;8:ZC09–12.
82. Dillenburg CS, Martins MA, Almeida LO, Meurer L, Squarize CH, Martins MD, et al. Epigenetic modifications and accumulation of DNA double-strand breaks in oral lichen planus lesions presenting poor response to therapy. Medicine. 2015;94(30):e997.
83. Song SJ, Ito K, Ala U, Kats L, Webster K, Sun SM, et al. The oncogenic MicroRNA miR-22 targets the TET2 tumor suppressor to promote hematopoietic stem cell self-renewal and transformation. Cell Stem Cell. 2013;13:87–101.
84. D'Souza W, Saranath D. Clinical implications of epigenetic regulation in oral cancer. Oral Oncol. 2015;51:1061–8.
85. Reis PP, Tomenson M, Cervigne NK, Machado J, Jurisica I, Pintilie M, et al. Programmed cell death 4 loss increases tumor cell invasion and is regulated by miR-21 in oral squamous cell carcinoma. Mol Cancer. 2010;9:238.

86. Cervigne NK, Reis PP, Machado J, Sadikovic B, Bradley G, Galloni NN, et al. Identification of a microRNA signature associated with progression of leukoplakia to oral carcinoma. Hum Mol Genet. 2009;18:4818–29.
87. Lod S, Johansson T, Abrahamsson KH, Larsson L. The influence of epigenetics in relation to oral health. Int J Dent Hyg. 2014;12:48–54.
88. Shridhar K, Walia GK, Aggarwal A, Gulati S, Geetha AV, Prabhakaran D, et al. DNA methylation markers for oral pre-cancer progression: a critical review. Oral Oncol. 2016;53:1–19.
89. Heyn H, Esteller M. DNA methylation profiling in the clinic: applications and challenges. Nat Rev Genet. 2012;13:679–92.
90. Ivanov M, Barragan I, Ingelman-Sundberg M. Epigenetic mechanisms of importance for drug treatment. Trends Pharmacol Sci. 2014;5:384–96.
91. Cantley MD, Bartold PM, Marino V, Fairlie DP, Le GT, Lucke AJ, et al. Histone deacetylase inhibitors and periodontal bone loss. J Periodontal Res. 2011;46:697–703.
92. Cantley M, Fairlie DP, Bartold PM, Rainsford KD, Le GT, Lucke AJ, et al. Compounds that inhibit histone deacetylases in class I and class II effectively suppress human osteoclasts in vitro. J Cell Physiol. 2011;22:22684.
93. Kim TI, Han JE, Jung HM, Oh JH, Woo KM. Analysis of histone deacetylase inhibitor-induced responses in human periodontal ligament fibroblasts. Biotechnol Lett. 2013;35:129–33.

The Relationship Between Periodontal Diseases and Chronic Diseases

Fábio Renato Manzolli Leite and Gustavo Giacomelli Nascimento

Contents

25.1 Introduction – 381

25.2 Biological Plausibility and Conceptual Models – 381

25.3 Temporality as an Issue – 381

25.4 A Glance into Confounding and Mediation – 382

25.5 The (Almost) Neglected Case of Collider Variables – 383

25.6 The Role of Smoking in the Association Between Periodontal and Systemic Diseases – 383

25.7 Biological Plausibility of the Association Between Periodontitis and Systemic Diseases – 384

25.7.1 Direct or Indirect Mechanisms? – 385

25.7.2 Periodontitis and Cardiovascular Disease – 385

25.7.3 Periodontitis and Adverse Pregnancy Outcomes – 387

25.8 Biological Plausibility of the Association Between Systemic Diseases and Periodontitis – 387

25.8.1 Obesity and Periodontitis – 388

25.8.2 Metabolic Syndrome (MetS) and Periodontitis – 388

25.9 Diabetes: The Issue of Diabetes and the Claim for a Bidirectional Relationship – 389

25.9.1 Evidence: Periodontitis and Diabetes – 389

25.9.2 Evidence: Diabetes and Periodontitis – 390

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_25

25.10 Other Features That May Influence the Association Between Periodontal and Systemic Conditions – 390
25.10.1 Hawthorne Effect – 390
25.10.2 Compliance Bias – 391
25.10.3 Sample Size Bias – 391
25.10.4 Misclassification Bias – 391
25.10.5 Attrition Bias – 391
25.10.6 Admission Rate Bias – 391
25.10.7 Allocation Bias – 391
25.10.8 Lack of Blinding – 391

25.11 Conclusion – 391

References – 392

Learning Objectives

- To point out the main methodological issues in the association between periodontitis and systemic diseases
- To examine the claim for a bidirectional relationship between periodontitis and systemic diseases
- To present the biological mechanisms underlying the relationship between periodontitis and systemic diseases and how they influence the study design and data analysis
- To assess the level and the quality of the evidence in the potential association between periodontitis and systemic diseases
- To point directions for future study design and data analyses in order to explore the potential relationship between periodontitis and systemic diseases

25.1 Introduction

Since the establishment of the germ theory in the 1900s, the periodontal field has been flooded with studies trying to identify and/or isolate causes of periodontal diseases. As diseases were expected to result from infections [1], such a thought was directly applied in the periodontal field. For decades, there was a quest to identify the keystone pathogen responsible for the occurrence of both gingivitis and periodontitis. With the isolation of the so-called putative periodontopathogens, the field moved toward a new course called "periodontal medicine." Despite the name, this new field was not a complete novelty. Instead, it revisited the "focal infection theory," which has been firstly advocated in dentistry by Weston Price back in 1925 [2]. According to this theory, bacteria and their by-products from periodontal lesions could gain entry into the circulatory system and cause diseases in distant sites. As a result, the number of publications regarding the association between periodontal diseases and systemic conditions is on the rise since the 1980s. Currently, more than 50 different conditions have been associated with periodontitis, and this number keeps increasing year after year [3]. However, as association does not necessarily imply causation, it is difficult to assume causal relationships between all pointed conditions.

The relationship between periodontitis and systemic diseases has been often described as being bidirectional. Nevertheless, as the study design of most studies on the topic precludes the identification of a directionality, associations are bidirectional by default, until proper data emerge to clarify the relationship. One may speculate whether the use of complex analytical approaches can compensate issues related to the study design and the quality of the data. However, no analytical software can determine, for instance, which one, periodontitis or diabetes, occurred first in time, or why clinical attachment loss should be preferred over probing depth. As Shakespeare once said, "all that glitters is not gold," and that is especially valid when looking at the relationship between periodontitis and systemic diseases.

Before formerly exploring the association between periodontitis and systemic diseases, we should further examine some methodological aspects that influence the findings from the studies on the periodontitis and systemic diseases relationship.

25.2 Biological Plausibility and Conceptual Models

Prior to inferring causal relationship between exposure and outcome, one must consider few assumptions further described in the Chap. [16]. Concisely, it is important to respect two items of the Bradford Hill criteria [4]. First, the cause must always precede the effect and secondly, a plausible biological theory must exist to explain the relationship. Even if the mechanisms are not completely understood, it is possible to distinguish whether plausibility makes sense or not. An example is the association between dental flossing and obesity [5]. In the study, the lack of daily dental flossing was associated with a dose-dependent increase in the body mass index. An extrapolation to the causal-inference field could generate headlines such as "floss and lose weight" [5]. Critically thinking, we shall consider that oral and general health awareness walk alongside, i.e., it is expected that if one increases so does the other, and vice-versa. The lack of well-conceived conceptual models may result in spurious associations. It is important to emphasize that since conceptual models follow the current knowledge, they can be valid in the current time and become inappropriate or incomplete with knowledge development.

The conceptual model should be established as an initial step, which will guide the selection of the most appropriate study design, variables (e.g., exposure, outcome, confounders, and mediators), and data analyses.

25.3 Temporality as an Issue

As mentioned before, the exposure has to precede the presumed outcome. This point brings us back to the discussion of study designs. In this chapter, studies will be split into observational and interventional, and the role of time will be addressed as retrospective or prospective.

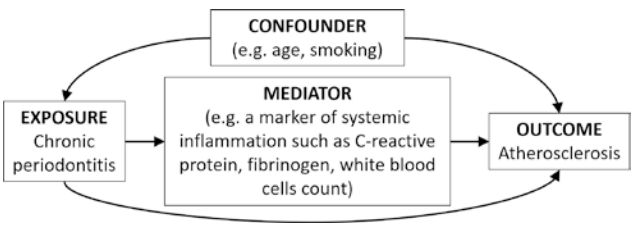
In retrospective studies, data are obtained from the past, e.g., from records or by interviewing the participant. Temporality between exposure and outcome may not be easy to determine and bias, mostly recall bias, may be introduced. In addition, the larger the temporal gap between cause and event, the harder it is to minimize the effect of confounding factors. In prospective studies, individuals are followed from that date onward, and all (or the majority) of data are collected along the study. Some types of biases, such as recall bias, are less prone to be introduced in studies with prospective design. Moreover, usually the temporal assumption that the exposure preceded the disease is easier to identify, which may support further studies on causation.

Observational study designs are the most frequently used to assess the relationship between periodontitis and systemic conditions. In such case, researchers observe the disease occurrence without any type of intervention. The cross-sectional design is by far the most employed, but for some conditions [e.g., cardiovascular diseases (CVD) and diabetes] case–control and cohort designs can also be identified, even though scarcely. The problem with cross-sectional studies is that exposure and outcome are measured concurrently, thus the temporal assumption is frequently violated [6–8]. Most of these investigations performed secondary data analysis, which used data with poor quality on the exposure, outcome, covariates, colliders, moderators, confounders, and/or mediators.

Interventional studies on the periodontal and systemic connection are normally prospective in the form of randomized clinical trials (RCTs) and aim to evaluate the effect of periodontitis treatment on a specific systemic condition. In a successfully randomized trial, it is expected all groups to be similar in all aspects, including measured and unmeasured confounders and, therefore, exchangeable. In a two-arm RCT for example, while one group receives an intervention, the other does not. In principle, along the whole study, the only difference among groups should be the intervention. All participants should be analyzed at the same time-points and receive the same examination procedures. As both groups are exchangeable, different results are assumed to be a consequence of the intervention. Extra methodological aspects should be considered to increase the quality of RCTs, such as blinding, allocation concealment, compliance and dropout evaluation, awareness for co-interventions, and intention to treat analyses. As the reader must have realized, RCTs need a long time between conceptualization and data analyses. Since RCTs require long time to produce results (which may not be the expected ones a priori), staff, organization skills, recruitment of several participants, knowledge of statistics, and financial resources, RCTs have not been the most used study design to explore the association between periodontal diseases and systemic conditions. Furthermore, not all conditions can be allocated to an RCT. For instance, if one aims to evaluate the effect of diabetes on periodontitis, it is not possible to allocate individuals to develop diabetes and monitor their periodontal conditions. Therefore, in such cases, well-conducted prospective longitudinal observational studies seem to be a realistic and useful alternative to address the issue of causality in the relationship between periodontitis and systemic diseases.

25.4 A Glance into Confounding and Mediation

As stated before, a conceptual model should guide the study design and the data analyses. It is not the purpose of this section to deepen into the role of each variable in the analytical models, however, the concept of mediation and confounding should be briefly presented, as these may influence the relationship between periodontitis and systemic diseases. A mediator is a variable that stands between the exposure and the outcome in the causal pathway. For this reason, this variable is highly influenced by the exposure, and in turn, influences the outcome. Although the concept of mediation is well known in the field, most studies do not deal properly with this issue. The use of conventional regression, the most common method used in the periodontitis–systemic disease studies, does not account appropriately for mediation, and therefore, may lead to biased estimates. Confounder is a term used to describe a variable, which is associated with both outcome and exposure, but is not part of the causal chain(◘ Fig. 25.1). For further information on mediation, please read the chapter "Causal inference in oral health epidemiology".

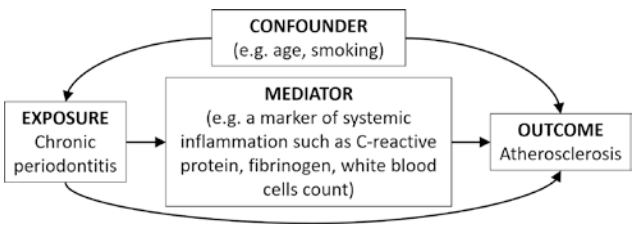


◘ **Fig. 25.1** Simplified conceptual model of the relationship between periodontitis (exposure) and atherosclerosis (outcome). Here, we hypothesize that periodontitis leads to systemic inflammation (mediator), which subsequently causes atherosclerosis. Confounders are determined on the basis of variables influencing both exposure and outcome, in this case, age, tobacco smoking habits, and others

25.5 The (Almost) Neglected Case of Collider Variables

A collider variable, or simply a collider, is causally affected by at least two variables. In most cases, a collider is a mediator, as it stands in the causal pathway between the exposure and outcome, and therefore, influences the relationship between exposure and outcome. The problem is that by conditioning on a collider in conventional regression analysis, in sample stratification, or when designing an experiment for example, researchers will likely fall into one of the many existing paradoxes, e.g., the obesity, Berkson's, and Simpson's paradoxes. When exploring potential causal relationships, conditioning on a collider usually induces an association where none exists [9]. An example of collider bias is likely to be observed in studies exploring the association between periodontitis and cardiovascular disease. Most of the studies use a type of selection bias known as collider stratification bias. In such case, having periodontitis and cardiovascular disease affects the inclusion into the study or into the analysis [9].

In ◘ Fig. 25.2, it is hypothesized that chronic periodontitis is associated with an increase in the systemic levels of inflammatory markers, and that these markers are predictors of atherosclerosis development. In addition, periodontitis can directly influence atherosclerosis risk. Currently, unmeasured common causes of systemic inflammation and atherosclerosis have to be assumed to play a role in the model (e.g., genetics, physiology, and behaviors). In this case, systemic inflammation is a collider, and the "paradox" results from studies that have adjusted for systemic inflammation (collider) in conventional regression analysis. Since bias occurs due to stratification on a collider, this selection bias is also known as collider stratification bias. Therefore, conventional analysis that do not account for the specificities of mediation, tend to distort the relationship between periodontitis and any systemic disease, and induce collider bias, which will ultimately lead to a "paradox."



◘ **Fig. 25.2** Simplified directed acyclic graph representing causal relations between periodontitis, systemic inflammation, atherosclerosis, and unmeasured confounder

► **Example**

Using data from the Pelotas 1982 birth cohort, it is possible to see the effect of collider bias in the association between periodontitis and carotid intima-media thickness (cIMT), a subclinical indicator of cardiovascular disease, having levels of C-reactive protein (CRP) as a mediator. Using conventional regression analysis, which does not properly account for mediation, periodontitis statistically significantly increased the odds of IMT in 54%. Stratified analysis by the levels of CRP revealed that in individuals with periodontitis and CRP >3 mg/L, the odds of IMT were 2.2, therefore, explaining the association. Nevertheless, when marginal structural modeling was used, an analytical approach that deals with mediation, the association between periodontitis and IMT vanished. Accordingly, it is possible to conclude that in this population, the association between periodontitis and IMT was a statistical phenomenon, rather than a causal relationship. ◄

25.6 The Role of Smoking in the Association Between Periodontal and Systemic Diseases

Before moving forward, one of the most discussed topic in the association between periodontal and systemic diseases is the possibility of removing residual effects of smoking using statistical methods. The reader should bear in mind all the following points when reading the scientific evidence we will present in the upcoming sections.

Smoking behavior patterns have been related to lifestyle, health awareness, socioeconomic status, level of education, and others. If not all, most of these factors, including tobacco smoking, have also been associated with the development of systemic conditions and periodontitis. As one would expect, most of the systemic diseases associated with tobacco smoking have also been associated with periodontitis. Therefore, smoking has been considered by decades a strong confounder in the periodontal-systemic association. Statistical adjustments attempt to remove the effect of smoking of the population and make the groups comparable regarding exposure to smoking along the life course.

Most of the studies attempt to capture all the dimensions of the smoking behavior using self-reported questions or, in a lower scale, determining the occurrence of other smoking-related systemic diseases, such as cancer development or respiratory diseases development. The information is then transformed into a variable containing two or three categories: smoker, nonsmoker, and/or never smoker. However, a categorized variable does not measure all dimensions

of the detrimental effects of smoking in a life course, information on the amount and length of exposure to tobacco, chemical composition of smoke, use of filter, and time since smoking cessation, among others must be included in the analysis. We should also consider the social undesirability in reporting smoking habits, the inaccuracy of remembering the average number of cigarettes consumed in the past months/years (recall bias), and so on. It may be clear now the reasons to assume that adjustment for smoking habits are most likely insufficient. If we combine this information with the known higher incidence of periodontitis among smokers, one can assume that the incidence and effect size of smoking-associated systemic diseases will always be higher in the periodontitis group. Given that, some authors advocate for the need to analyze the periodontitis association with systemic diseases in never-smokers, since it is practically impossible to eliminate the residual effect of smoking [10, 11].

Researchers in the field of obesity were one of the first to argue for a primary data analysis considering only never-smoking subjects. In such case, smoking and obesity association cannot be isolated from the effect of smoking on illness and mortality [12].

Hujoel and collaborators [11] used data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study (NHEFS) to exemplify the importance of the quality of data on smoking habits to assess the existence and the magnitude of periodontitis and systemic disease associations (Table 25.1).

The effect of smoking in the development and progression of several diseases is high, is cumulative, and has a biologic gradient (the more one smokes, the higher the effect of smoking). Therefore, investigators must be very cautious when exploring the association between two conditions that are both associated with smoking. As demonstrated in Table 25.1, the poorer the control for smoking, the higher the chance that periodontitis will reproduce the direction and strength by which smoking is associated with the explored systemic condition. Profound analyses of the effect of smoking in the reported associations between periodontal and systemic diseases are out of the scope of this chapter.

One should remember that the data quality for factors known to influence both periodontitis and systemic diseases (such as smoking, education, and SES) is of ultimate importance to minimize the effect of residual confounders and the chance of spurious findings.

Table 25.1 Adjustment for tobacco smoking and the magnitude of periodontitis–systemic disease associations (reused with permission from John Wiley and Sons) [11]

Disease	Excellent[a]	Good[b]	Poor[c]
COPD[d]	1.24 (0.90–1.72)	1.42 (1.16–1.72)	1.52 (1.21–1.91)
Lung cancer[e]	0.58 (0.12–2.78)	1.48 (0.88–2.50)	1.94 (1.14–3.30)
Stroke[f]	1.11 (0.79–1.57)	1.09 (0.82–1.45)	1.19 (0.84–1.73)
CHD[g]	1.04 (0.82–1.32)	1.13 (0.95–1.34)	1.26 (1.02–1.56)

[a]Excellent control for smoking refers to analyses limited to never-smokers

[b]Good control for smoking was obtained by including smokers in the analyses (~50% of the population) and adjusting the analyses for the logarithm of smoking duration and the number of cigarettes per day

[c]Poor control for smoking was obtained by limiting the analyses to smokers and not adjusting the analyses for smoking duration or dose

[d]COPD, chronic obstructive pulmonary disease (analyses were adjusted for age, age squared, race, poverty index, education, smoking duration and dose, and vitamins A and C)

[e]Lung cancer (analyses adjusted for the same variables as COPD analyses)

[f]Stroke (analyses were adjusted for same variables as CHD analyses)

[g]CHD, coronary heart disease [analyses adjusted for age, age squared, gender, race (two indicator variables for African American and other), poverty index, marital state, education, and an interaction term for marital state and gender, diastolic blood pressure, systolic blood pressure, serum cholesterol, diabetes, log (height), log (weight), log (number of glasses per day), physical activity (indicator variable for heavy recreational or nonrecreational physical activity), and nervous breakdown and sampling design]

25.7 Biological Plausibility of the Association Between Periodontitis and Systemic Diseases

As stated before, one of the criteria to propose a potential causal relationship between exposure and outcome is the existence of a reasonable biological plausibility. Most of the mechanisms used to explain the relationship between periodontitis and chronic systemic diseases are summarized in Fig. 25.3. Bacteria and their toxins (such as endotoxins) may gain entry into the bloodstream through swallowing and gingival blood capillaries (events called bacteremia and endotoxemia).

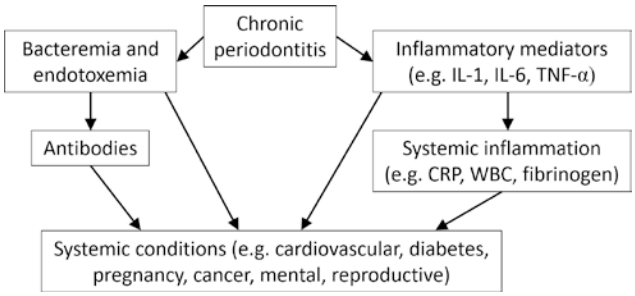


Fig. 25.3 Simplified model of the main theories relating chronic periodontitis and systemic conditions. The biological plausibility for some of the shown mechanisms varies according to the systemic condition. IL interleukin, TNF tumor necrosis factor, CRP C-reactive protein, WBC white blood cells

Systemic effects may be observed by direct activity of bacteria and their by-products on the tissues or by the production of antibodies against them. Autoantibodies can be generated via molecular mimicry, and signalize that some host structures should or may be attacked (e.g., tissues in joints, blood vessels, uterus, brain and others) [13]. Proinflammatory mediators, such as interleukin (IL)-1, prostaglandins, and tumor necrosis factor (TNF)-α, from periodontal lesions may induce especially the liver to produce a systemic low-grade inflammation.

Obviously, the reader must be aware that some pathways shown in Fig. 25.3 may present a stronger or weaker biological plausibility or scientific evidence according to the condition under examination. One can also depict that this model can or has been used to associate periodontitis with any systemic condition regardless of a critical judgment.

25.7.1 Direct or Indirect Mechanisms?

The association between periodontal diseases and chronic systemic conditions has been ruled by two mechanisms, which can occur concomitantly for some conditions (Fig. 25.3).

- Direct mechanism: as periodontitis develops, the periodontal pocket epithelium continuity is lost and an ulcerated epithelium is observed. Due to the intimate contact of the subgingival biofilm with the connective tissue, periodontal bacteria and their products (e.g., lipopolysaccharide) can now gain entry into the circulation and act directly in distant organs and tissues. In addition, bacteria could be swallowed and could gain entry into the circulation. In sum, constant bacteremia and endotoxemia could be considered the exposure.
- Indirect mechanism: the chronic release of inflammatory mediators from periodontal lesions into the circulatory system would induce a systemic inflammation, which would increase the risk for a determined systemic condition.

▶ Example

Shortly, in theory, periodontitis could influence atherosclerosis development in different ways. Directly: Periodontopathogens may enter the circulation and initiate or increase the development rate of atherosclerotic plaques. (B) Indirectly: Proinflammatory mediators from periodontal lesions induce the production of proatherogenic molecules (C-reactive protein, fibrinogen, low-density lipoprotein, etc.), which consequently would affect the progression or rupture of atherosclerotic plaques. ◀

25.7.2 Periodontitis and Cardiovascular Disease

The term cardiovascular diseases (CVD) encompasses multiple conditions that affect the heart and the vessels of the circulatory system. The most frequently studied disorders are the coronary heart diseases, which by partial or complete blockage of the coronary arteries cause angina and myocardial infarction, and stroke which results from reduced/interrupted blood flow or hemorrhage in the cerebral circulation. It is difficult to include all CVDs into one package, assuming they all possess the same etiological and risk factors. The most explored common risk factors are tobacco smoking, hypertension, hyperlipidemia, and obesity. Because CVDs are the leading cause of death in the world [14], the identification of other causes is of public health importance.

In theory, periodontitis has been implicated in different ways with occurrence of CVDs (Fig. 25.4). In a direct mechanism, periodontal bacteria gain entry into the circulatory system and act in the endothelial tissue and/or in the atherosclerotic plaque. In an indirect mechanism, bacterial by-products could lead to autoantibodies generation by molecular mimicry or by alteration in the ratio between low-density lipids (LDL) and high-density lipids (HDL). In addition, proinflam-

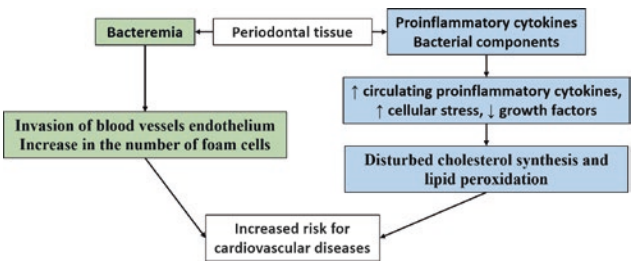


Fig. 25.4 Overview of the main proposed pathways relating chronic periodontitis and cardiovascular diseases. Direct effect (green pathway): periodontopathogenic bacteria gain entry into the circulatory system and affect blood vessels or atherosclerotic plaques. Indirect effect (blue pathway): proinflammatory cytokines and/or endotoxins from periodontal lesions gain entry into the circulation contributing to systemic low-grade inflammation. The atherogenic lipid profile worsens and increases the risk for CVD

matory cytokines or reactive oxygen species produced in periodontitis lesions could affect cholesterol synthesis and lipid peroxidation [15]. Most of these theories originated from in vitro and animal studies, and to date, the interaction between cells of the connective and bone tissue in the periodontium with periodontopathogenic bacteria has not been shown in vivo [16].

A systematic review by The Cochrane Collaboration [17] evaluated the effect of periodontal therapy in the management of CVD. Two types of prevention studies were searched, primary prevention investigations that use periodontal therapy to prevent CVD in people without CVD. In secondary prevention studies, participants have been diagnosed with CVD and are treated for periodontitis. The authors could not identify any study focusing on primary prevention. For secondary prevention, they identified only one RCT of very low quality [17, 18]. Current evidence on the effect of periodontal therapy on reducing the risk of CVD recurrence in people with chronic periodontitis is insufficient (RR 0.72; 95% CI 0.23–2.22).

Different reasons can be pointed as causes for the inexistence of a RCT with focus on primary intervention. The major point is the length of a RCT when dealing with two chronic slow-developing/progressing diseases. The need to use many years and multiple centers to evaluate a causal-relationship demands lots of money, e.g., with staff, infrastructure, clinical, and laboratorial analyses. Considering also the rise in dropout rates as the follow-up time increases, the RCT will demand large sample size, which again will require more resources. Although studies have tried to reduce sample size by restricting inclusion and exclusion criteria, limited eligibility criteria may preclude results that mimic real life situations, and thus, become useless. Another point is the ethical need to provide proper treatment for both control and intervention groups, which may change the size of the effect. In this case, if periodontal treatment is to have an effect on CVD risk, it is probably small in the constellation of risk factors for CVD. Therefore, a very large sample will be required to detect an effect. In this context, population databases, which include medical and dental data, are required to explore properly the issue.

Another attempt in the medical and dental fields to overcome the issue of long follow-up and expensive trials when dealing with chronic diseases is to use surrogate endpoints. A surrogate endpoint should be a substitute for a clinical endpoint and must predict clinical benefit. An example can be a trial with a therapy that aims to reduce C-reactive protein or HDL levels as a means to prevent CVD. Previous reports have shown that despite the benefits on the targeted endpoint, clinical outcomes were not affected [19]. Reasons might be that the surrogate is not in the causal pathway, the therapy causes side effects on other surrogates or that other surrogates or pathways may be as or more important than the investigated surrogate, which might have overshadowed the effect of the intervention. At least half of the trials verifying whether the intervention on specific surrogate endpoints were translated into benefits for clinical outcomes did not confirm the findings [19, 20]. In any case, periodontal therapy may have multiple effects, which may not translate directly into a systemic clinical outcome, however, if a positive effect on a surrogate is observed, it is worth pursuing the promotion of periodontal health for the sake of the overall patient's health. The important message for researchers is to take an extra care to extrapolate potential benefits for clinical outcomes just based on modification of surrogate endpoint levels.

25.7.2.1 Evidence

Most of the studies published on the topic share similar issues considering other factors that confound the relationship between periodontitis and CVD. The major problems are the poor-quality information on smoking along the life course; the higher number of smokers among participants with periodontal disease; the higher number of participants with low socioeconomic status and/or low level of education in the group with CVD; the restricted access to medical/dental care among the group with systemic disease. In the vast majority of the studies included in the latest systematic reviews on the topic, these factors were not properly adjusted for. Probably, after correct adjustment, the little-to-moderate effect, if present, would probably disappear.

Even though recent systematic reviews have demonstrated an association between periodontitis and increased carotid intima-media thickness and worst endothelial function (arterial stiffness measured by pulse wave velocity – PWV), their results need to be carefully analyzed [21, 22]. Considering all the points mentioned about the use of surrogate endpoint markers, and knowing the lack of consistency of CRP in predicting CVD [20], the evidence that periodontitis treatment improves CRP levels will not be addressed in this chapter [23]. It is worth mentioning, that even considering results with poor adjustment for main confounders, improvements were overall nonexistent or small.

The study on arterial stiffness [21] observed that people with periodontitis have increased PWV compared to controls (mean difference 0.85 m/s; 95% CI 0.53–1.16). It is important to mention many limitations of the studies included in the quantitative analyses. Out of the seven studies included in this systematic review, one was an RCT, one was a case–control study, and five were cross-sectional studies. The only interventional study found no difference in PWV measurements between the groups up to 12 months of intervention; however, the

study was conducted in an aboriginal population with many other health comorbidities. Generally speaking, analyses were poorly controlled for smoking habits (usually, current smoker or not), socioeconomic status were not considered, and data regarding other comorbidities (such as diabetes) were neglected. Not surprisingly, all the included studies presented low level of evidence according to the authors. Finally, the different methods of assessing periodontal disease and PWV introduced heterogeneity in the results. Therefore, caution should be taken before assuming an association between periodontal diseases and arterial stiffness.

A recent systematic review showed a mean increase of 0.08 mm (95% C.I. = 0.07–0.09) in cIMT associated with periodontitis [22]. The authors identified ten cross-sectional and seven case–control studies. However, studies suffered from the same limitations mentioned for PWV, mainly poor or lack control for good-quality data on smoking, negligence of socioeconomic background, and other comorbidities. Periodontitis and cIMT progression share many risk factors or causes, such as age, sex, blood pressure, cholesterol, smoking, and diabetes. As mentioned by the authors, considering the absence of adjustment for all these confounders in the majority of the studies included in their meta-analysis, the accuracy of the results may be questioned. Consequently, it is challenging to ascertain a potential influence of periodontitis on cIMT development/progression.

Finally, two recently published studies are worth mentioning. The first study attempted to verify whether periodontitis could be used as a predictor of poor outcome of lacunar infarct in a case–control study [24]. Similar methodological issues from the cIMT and periodontitis association were found in this study. The group with lacunar infarct tended to present more people with diabetes, hypercholesterolemia, and history of alcohol and tobacco consumption. One may question that although some of these characteristics did not statistically differ between groups, it is known that, when combined, factors increase their effect in a multiplicative, rather than additive scale. Therefore, the borderline association (OR = 1.1, 95% CI: 1.0–1.1) between periodontitis and lacunar infarct after adjustment for some confounders, may still represent the effect of residual confounders such as smoking and diabetes. The second study used a prospective longitudinal population-based cohort design to verify the association between periodontitis and incident venous thromboembolism [25]. The study relied on considerably good data on background confounders (even though smoking was categorized just as current, former and never) from 8092 participants, followed for a mean time of 12 years. After adjustment for the main confounders, no statistical association was observed.

25.7.3 Periodontitis and Adverse Pregnancy Outcomes

Since early 2000s, the association between periodontitis and adverse pregnancy outcomes (APO) has been intensively investigated in the dental field. While several studies found a positive association between periodontitis and preeclampsia, low birth weight and preterm delivery, a large number of other studies failed to confirm these results.

It has been hypothesized that both direct and indirect mechanisms link periodontitis to APO. Spread of key periodontopathogens (especially *P. gingivalis* and *F. nucleatum*) and their by-products in the blood stream, and subsequent seeding of the placental membranes has been proposed as a potential direct mechanism. Indirectly, periodontitis leads to an increase in the levels of prostaglandin E2 and proinflammatory cytokines, such as TNFα and IL-1β, which in turn induce rupture of the amniotic sac membranes, uterine contraction, cervical dilation, and ultimately delivery.

In an overview article of systematic reviews, Daalderop and colleagues [26] concluded that the "association between periodontal disease and severe adverse pregnancy outcomes is now sufficiently established." However, the authors' conclusion is based on several systematic reviews that share common limitations related to the lack of adjustment for confounding. Confounders such as smoking, socioeconomic status, and maternal age have not been properly addressed, what might have led to overestimated, and therefore, misleading results.

A Cochrane systematic review failed to find an effect of periodontal therapy on the prevention of APO [27]. Although 15 randomized controlled trials were included in the review, the available evidence was evaluated as either of very low or low quality. Lack of blinding of participants, imbalance in baseline characteristics, lack of periodontal data at follow-up, and considerable attrition rates are among the main limitations of the studies included in the review. Based on their findings, the authors concluded that there is insufficient evidence to support a beneficial effect of periodontal therapy on APO.

25.8 Biological Plausibility of the Association Between Systemic Diseases and Periodontitis

In this section, we will examine the biological plausibility underlying the hypothesis that systemic diseases may influence the onset and progression of periodontitis. Several reasonable mechanisms explain these con-

nections. Individuals suffering from systemic diseases have a chronic immune system activation with increased levels of circulating leukocytes and proinflammatory markers. This sustained systemic low-grade inflammation would promote alterations in the periodontal tissues, which would lead to its breakdown.

Note that systemic inflammation can be used to explain the association between most of the systemic conditions and periodontitis. Thus, critical sense is necessary in order to judge the real plausibility of a potential association.

25.8.1 Obesity and Periodontitis

Several studies have pointed out an association between obesity and periodontitis. The excessive adipose tissue, by downgrading adiponectin levels, creates a reservoir of proinflammatory cytokines, which in turn, induce a chronic systemic inflammation. In addition, the expansion of the adipose tissue constraints blood vessels, and adipocytes located in the core of the adipose tissue die due to hypoxia. This local inflammation contributes to the secretion of proinflammatory cytokines, and thus, exacerbates the systemic inflammatory frame. Additionally, obesity may also affect the immune response in the periodontium, by attenuating macrophage infiltration and activation.

25.8.1.1 Evidence

In a meta-analysis of population-based longitudinal prospective studies, Nascimento et al. [28] indicated that obesity and overweight increased in 34% and 13% the risk of periodontitis, respectively. Nevertheless, the authors clearly stated that these findings should be carefully considered, as the evidence originated from few studies conducted in high-income countries. In addition, all studies used probing pocket depth to diagnose and monitor periodontitis, and therefore, the effect of obesity on periodontal destruction could not be measured. Finally, some studies included in the review enrolled young individuals and comprised a relatively short follow-up, given the chronicity of both obesity and periodontitis. On a similar note, Gaio et al. [29] found that obese individuals had 36% risk of experiencing periodontal attachment loss in a 5-year prospective study conducted in Southern Brazil, with a greater risk among women than men. Even though this study measured periodontal destruction, it also relied on a short follow-up. Using data from the 1982 Pelotas birth cohort, Nascimento et al. [30] simulated hypothetical scenarios using causal inference analytical approach to estimate the effect of life-course obesity on periodontitis in adulthood. The authors found that life-course obesity and overweight increased the risk of periodontitis in adulthood, and when combined with health detrimental habits (smoking, alcohol, and diet) the risk of periodontitis was even greater. However, the authors' findings should not be extrapolated to other populations, as the analytical approach employed calculates the risk based on the distribution of covariates for the specific population. This relationship was further examined by Shungin et al. [31], by using Mendelian randomization analyses, who did not find a causal relationship between obesity and periodontitis in a sample of 50,000 individuals from 13 studies from Europe and the USA. Although the authors have used genetic association analysis, biological confounding could not be ruled out due to multiple differences in data collection.

25.8.2 Metabolic Syndrome (MetS) and Periodontitis

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that include dyslipidemia, insulin resistance, abdominal obesity, and hypertension. The biological mechanisms underlying the relationship between metabolic syndrome and periodontitis relate to increased levels of proinflammatory cytokines and oxidative stress, as results from the combination of several systemic conditions that constitute the metabolic syndrome [32].

25.8.2.1 Evidence

The association between metabolic syndrome and periodontitis has been examined by several epidemiological studies. Accumulated evidence on the topic revealed that MetS is positively associated with periodontitis, but the high heterogeneity found in the meta-analysis was mainly a result of controversial results between studies. In addition, most of the studies conducted on this topic have a cross-sectional design, which, as aforementioned in this chapter, prevents from the establishment of temporal and causal relations. Evidence from prospective longitudinal studies on this relationship is scant. In a study conducted among veterans in the USA, Kaye et al. [33] found that periodontitis progression and onset were higher among individuals with MetS. Nevertheless, males mostly from Caucasian origin composed the study sample, and therefore, the generalization of these findings to more diverse populations is precluded. In a birth cohort study, Nascimento et al. [34] identified a positive association between MetS and severe cases of periodontitis. However, the authors could not evaluate the impact of MetS on the progression of periodontitis, due to lack of a periodontal follow-up.

25.9 Diabetes: The Issue of Diabetes and the Claim for a Bidirectional Relationship

A two-way relationship between diabetes and periodontitis has been proposed. Figure 25.5 depicts a simplified version of the potential mechanisms involved in the bidirectional association between periodontitis and diabetes.

Periodontitis mainly results from the release of proinflammatory cytokines by local periodontal cells. It has been advocated that these cytokines and periodontopathogens gain entry into the circulatory system and contribute to the existing low-grade systemic inflammation in people with diabetes. Higher levels of circulating WBC, IL-6, and TNF-α can aggravate insulin resistance/release and impair glycemic control [35]. One potential explanatory mechanism is that neutrophils produce TNFα that may interact with insulin signaling pathways and beta cell function [35]. In addition, dyslipidemia can increase the oxidative metabolism of cells, with overproduction of reactive oxygen species. Therefore, damage to lipid membranes and DNA, enzymes oxidation, and further increase in cytokines levels may be observed.

On the other direction, hyperglycemia induces the production of proinflammatory molecules that will act on the periodontal tissues. Neutrophils in individuals with diabetes have an elevated respiratory burst associated with delayed apoptosis. Some authors have observed a binding of advanced glycation end products with their receptors in the periodontal tissues of patients with diabetes, which potentially results in cytokine release and altered inflammatory responses. In those subjects with further adipose tissue proliferation, adipokines induce inflammatory cytokine production, e.g., TNF-α and IL-6 [36].

25.9.1 Evidence: Periodontitis and Diabetes

A Cochrane systematic review of randomized clinical trials (RCTs) published until December 2014 included 14 studies compiling data from 1499 participants with diabetes [37]. The RCTs compared two groups, one that received periodontal therapy and another in which no intervention was performed. Pooled estimates of low-quality evidence revealed a mean reduction of 0.29% in glycated hemoglobin (HbA1c) levels (95% confidence interval (CI) −0.48 to −0.10) after 3–4 months post-treatment. However, no benefit for periodontal therapy was observed after 6 months of therapy (−0.02%; 95%CI −0.20% to 0.16%). The authors reported a considerable variability between studies, regarding especially age, follow-up period from 3 to 12 months, use of antidiabetic therapy, and baseline HbA1c levels from 5.5% to 13.1%. It is also important to mention that data on tobacco smoking were self-reported in the studies and categorized (usually as current, former and never smoker). As previously discussed in this chapter, residual confounding due to smoking could not be ruled out, especially when a poor definition of smoking was adopted. The Cochrane review made some recommendations that ought to be addressed in future studies as follows: need for at least 6-month follow-up after treatment completion; establishment of a control group; monitoring of antidiabetic therapy; sufficient sample size; clear definition of periodontitis and diabetes; and delivery of supportive therapy along the study to maintain the periodontal inflammation at low levels. Study design and randomization process must also consider participants age, time since diabetes diagnosis, type of antidiabetic medication, comprehensive assessment of smoking (e.g., length of exposure, amount, time since smoking cessation [7, 38]), HbA1c baseline values, and presence of diabetes-related complications.

A recently published RCT attempted to cover most of the limitations pointed out by the Cochrane review [39]. The design considered 12-month follow-up of people living with type 2 diabetes for more than 6 months, having moderate-to-severe periodontitis, and with at least 15 teeth. Exclusion criteria were uncontrolled systemic disease other than diabetes, chronic use of medications known to influence the periodontal tissue metabolism, hepatitis B and HIV infection, chronic systemic antibiotics use, and pregnancy or lactation. Clinical data comprised tobacco exposure (current, former, never smoker), blood pressure measure, body-mass index (BMI), and self-reported and/or prescription assessed medication data. One group (n = 133) received intensive periodontal treatment (IPT) consisting of nonsurgical and surgical periodontal therapy and supportive periodontal therapy every 3 months, while the other (n = 131) received control periodontal treatment (CPT) based on supragingival scaling and polishing. The authors found a mean reduction in HbA1c of 0.3% (95% CI 0.0 to 0.5) at 6 months and of 0.6% (95% CI 0.3 to 0.9) at 12 months in the IPT group compared with the CPT group. These results were adjusted for baseline HbA1c, age, sex, ethnicity, smok-

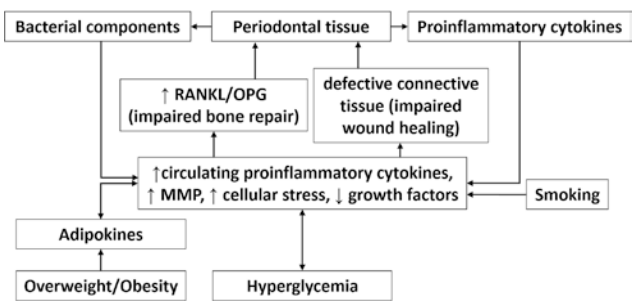


Fig. 25.5 Simplified scheme for the bidirectional relationship between periodontitis and hyperglycemia

ing status, duration of diabetes, and BMI. Nevertheless, socioeconomic status and educational level conditions that may nullify this relationship [40] were not considered in the study. In addition, the diabetes duration, the daily dose of insulin, and the extent of sites with periodontitis tended to be higher in the CPT group. Finally, the IPT group commenced the study with higher number of periodontal pockets >6 mm, and as well-known, individuals with greater levels of disease benefit the most from periodontal therapy, as explained by the "floor effect" phenomenon [40].

The scientific evidence with longer follow-up has a tendency to support a low-to-modest enhancement in glycemic levels after periodontal therapy in people with diabetes. Nevertheless, considering the caveats of current published studies, well-designed and conducted studies, with at least 12-month follow-up, substantial information on known confounders and adequate sample size is required to support the hypothesis of a relationship between periodontal diseases and diabetes.

25.9.2 Evidence: Diabetes and Periodontitis

The effect of diabetes on periodontitis has been explored in studies using both observational and interventional designs. Findings from observational studies provide evidence on the effect of diabetes on the onset and progression of periodontitis, whereas interventional studies contribute to the understanding of the effect of diabetes on response to periodontal therapy.

Even though the relationship between diabetes and periodontitis has been taken for granted, there are few prospective longitudinal studies on the topic. Nascimento and colleagues combined data from six prospective longitudinal studies in a meta-analysis [8]. The authors found that diabetes increased the risk for periodontitis by 86% after adjustment for confounders (RR 1.86 [95% CI 1.3–2.8]) [8]. Nevertheless, the authors pointed out several methodological issues in the studies included in the meta-analysis. Among the major issues, it is worth highlighting the lack of studies on the effect of diabetes on clinical attachment loss, that is, five of the six included studies used periodontal pocket depth to diagnose and monitor periodontitis, despite the fact that periodontal destruction is largely not followed by pocket deepening [41, 42]. In addition, most of the studies did not present adequate adjustment for relevant confounders, and information on smoking, for example, was mostly self-reported and included as a dichotomous variable (current or former/never smoker).

Data about the long-term effect of diabetes on the progression of periodontitis are scant. In a five-year small sample-sized case–control study, participants were matched for sex and self-reported smoking (current, past, or never smoker). According to their diabetes status, participants were split into three groups: poorly controlled diabetes; diabetes with good glycemic control; and nondiabetes. Variables associated with risk for periodontitis progression were bleeding on probing (BOP) in >30% of sites (odds ratio [OR] = 4.1), smoking (OR = 3.7), and poorly controlled diabetes (OR = 2.9). However, the risk for periodontitis progression was not dependent exclusively on the glycemic control, as higher risk for periodontitis progression was noted in the presence of an interaction between smoking and poorly controlled diabetes (OR 6.9).

To evaluate the effect of poorly controlled diabetes on periodontal response to therapy, Kocher and collaborators [40] pooled published data of RCTs from more than 50 groups. The authors found that before any adjustment, baseline levels of HbA1c were positively associated with mean pocket depth before and after periodontal therapy, that is, individuals with poorly controlled diabetes experienced more disease and poorer response to therapy than people without diabetes. However, the tendency for better results in pocket depth reduction and attachment level gain (response to periodontal therapy) in participants without diabetes disappeared after adjustment for age and sex. The authors, then, concluded that poor glycemic control had no effect on short-term results of periodontal therapy. In addition, they have shown that individuals with periodontitis and diabetes would achieve the same levels of pocket depth reduction and attachment gain. Irrespective of glycemic control, the main predictors for mean pocket depth reduction and attachment gain were the baseline periodontal measures.

25.10 Other Features That May Influence the Association Between Periodontal and Systemic Conditions

Different elements can act (alone or in combination) to induce a positive finding, they are all called biases. One of the most discussed is the distortion of results caused by confounding bias, which has been presented before. We very briefly describe some bias (but not all) that may distort the findings of a study.

25.10.1 Hawthorne Effect

In clinical trials, the Hawthorne effect may also play an important role. Participants modify their behavior because they know they are being observed. Different behaviors can be modified quickly with short-term results, such as exercise routine, dietary, and hygiene habits. Therefore, the results of an outcome can be modified

irrespective of the intervention. For example, imagine an RCT with people with diabetes where only one group receives periodontal therapy, the control group receives no intervention. There is a possibility that people in the treated group become more aware of their health and start to take better care of their overall health. Thus, improvements in the Hb1Ac may not be due to (or only to) periodontal therapy, but because participants started to exercise, to check their HbA1c levels properly, to change their dietary habits, or to comply better with an antidiabetic medication, for instance.

25.10.2 Compliance Bias

In trials that demand the participant's adherence to therapy, problems of efficacy are confounded with those of compliance, e.g., people with high-risk of periodontitis may comply less with maintenance therapy or diabetes control.

25.10.3 Sample Size Bias

Studies with small sample sizes have increased risk that observations will be due to chance, which is minimized by the use of larger sample sizes (wrong sample size bias). Conversely, larger studies sometimes detect small associations not clinically relevant and they amplify embedded biases.

25.10.4 Misclassification Bias

All participants have to be correctly classified according to their characteristics and the presence of exposure (e.g., having or not periodontal disease). Misclassification is present when the participant is allocated to an incorrect group/category. Consequently, this mistake can produce, for example, spurious associations between the exposure and the outcome. If the association does exist, this bias can distort the effect size. In systematic reviews, a common source of heterogeneity between the identified studies is the use of different classifications for periodontal disease, which will possibly lead to misclassification bias when the studies estimates are pooled in the meta-analysis.

25.10.5 Attrition Bias

This type of bias is also described as loss to follow-up (participants that abandon the study). If the attrition rates are different between the groups, the characteristics of the groups may change and influence the results independently of the intervention or exposure. In addition, results may not be generalizable to the population anymore, a problem observed sometimes in cohort studies.

25.10.6 Admission Rate Bias

Combining the exposure to certain risk factors and incidence of a disease increases the chance of a person to be admitted or referred to a specialized facility (e.g., hospital or a periodontal specialist). These cases may have higher risk exposures or disease compared to cases in the population in general. Therefore, if one designs a case–control study using these cases, one can find an association or distorted estimates between exposure and outcome.

25.10.7 Allocation Bias

If an investigator predicts or knows the intervention the next participant shall receive, it may affect the way potential participants are approached and their assignment to the groups. For example, participants with good compliance or prognoses can be allocated more into one group compared to another. In a RCT with people living with diabetes, the investigator can allocate participants with higher chance of compliance with the therapy to the group that will receive treatment, than to the control group that will not be treated.

25.10.8 Lack of Blinding

Blinding of the investigators and of the participants in the research is necessary to minimize bias introduced by knowing whether a participant is receiving an intervention or not. For some interventions, blinding can be applied to all levels of the people involved in the study (participant, staff, clinicians, data analyst, etc.). In some cases due to some trials characteristics or ethics, blinding may be only partial, for example, in trials comparing results from surgical and nonsurgical periodontal therapy, or oral hygiene products with different tastes. As an overall recommendation, blinding should be kept until final data analysis if possible.

25.11 Conclusion

The idea that chronic systemic diseases influence periodontitis (and vice versa) has emerged in the early 1950s. Since then, periodontal research has focused on the investigation of a causal relationship between hundreds of conditions. While statistical associations have been

found, a causal relation has not yet been proven for any condition. Methodological issues related to restricted sample size, lack of prospective longitudinal studies, and improper adjustment for relevant confounders, such as smoking and socioeconomic position, are shared among most of the studies on this topic. Therefore, investigators are strongly encouraged to follow best practices in study planning and data collection. To be more specific, studies with sufficient power, well designed, and with long follow-up are still necessary in order to clarify whether and to which extent systemic conditions impact on periodontal diseases onset and progression, and how beneficial periodontal treatment can be on the improvement of systemic disorders. To overcome the issue of smoking, future studies should consider the inclusion of never smokers to minimize the residual effect of tobacco exposure in the associations. Yet, beyond the advances in data analysis to adjust for smoking, several dimension of this behavior, as duration, frequency, and quantity are not properly addressed, and therefore, residual confounding cannot be ruled out. Thus, evidence on the association between periodontitis and any systemic condition should not be faced as "definitive."

Regardless of methodological issues, the proliferation of causal thinking in the periodontal field has motivated researchers to reflect upon the plausibility of the underlying relationship between chronic systemic diseases and periodontitis. It has also stimulated investigators to be more explicit and transparent concerning the conceptual framework and the methodological approaches chosen.

Irrespective of how meticulous a study is planned, it is highly unlikely that all methodological issues will be addressed. It is not realistic to expect a "perfect" scenario in which, for instance, there is no unmeasured confounding, and no measurement error. In the "real world," causal inference remains as a subjective process, given aspects of temporality and plausibility. Before making causal claims on the relationship between chronic systemic diseases and periodontitis, researchers are encouraged to apply not only rational judgment and technical expertise but mostly reasonable thoughts.

References

1. Gibbons RV. Germs, Dr. Billings, and the theory of focal infection. Clin Infect Dis. 1998;27(3):627–33.
2. Price WA. Dental infections and related degenerative diseases: some structural and biochemical factors. J Am Med Assoc. 1925;84(4):254–61.
3. Monsarrat P, Blaizot A, Kemoun P, Ravaud P, Nabet C, Sixou M, et al. Clinical research activity in periodontal medicine: a systematic mapping of trial registers. J Clin Periodontol. 2016;43(5):390–400.
4. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
5. Hujoel PP, Cunha-Cruz J, Kressin NR. Spurious associations in oral epidemiological research: the case of dental flossing and obesity. J Clin Periodontol. 2006;33(8):520–3.
6. Winning L, Linden GJ. Periodontitis and systemic disease: association or causality? Curr Oral Health Rep. 2017;4(1):1–7.
7. Leite FRM, Nascimento GG, Scheutz F, Lopez R. Effect of smoking on periodontitis: a systematic review and meta-regression. Am J Prev Med. 2018;54(6):831–41.
8. Nascimento GG, Leite FRM, Vestergaard P, Scheutz F, Lopez R. Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies. Acta Diabetol. 2018.
9. Banack HR, Kaufman JS. The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. Prev Med. 2014;62:96–102.
10. Spiekerman CF, Hujoel PP, DeRouen TA. Bias induced by self-reported smoking on periodontitis-systemic disease associations. J Dent Res. 2003;82(5):345–9.
11. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontitis-systemic disease associations in the presence of smoking – causal or coincidental? Periodontology 2000. 2002;30:51–60.
12. Peto J. Cancer epidemiology in the last century and the next decade. Nature. 2001;411(6835):390–5.
13. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15(1):30–44.
14. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1–25.
15. Merchant AT, Virani SS. Evaluating periodontal treatment to prevent cardiovascular disease: challenges and possible solutions. Curr Atheroscler Rep. 2017;19(1):4.
16. Bartold PM, Van Dyke TE. An appraisal of the role of specific bacteria in the initial pathogenesis of periodontitis. J Clin Periodontol. 2019;46(1):6–11.
17. Li C, Lv Z, Shi Z, Zhu Y, Wu Y, Li L, et al. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. Cochrane Database Syst Rev. 2014;(8):CD009197.
18. Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, et al. Results from the Periodontitis and Vascular Events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. J Periodontol. 2009;80(2):190–201.
19. Bikdeli B, Punnanithinont N, Akram Y, Lee I, Desai NR, Ross JS, et al. Two decades of cardiovascular trials with primary surrogate endpoints: 1990–2011. J Am Heart Assoc. 2017;6(3).
20. Force USPST. Risk assessment for cardiovascular disease with nontraditional risk factors: us preventive services task force recommendation statement. JAMA. 2018;320(3):272–80.
21. Schmitt A, Carra MC, Boutouyrie P, Bouchard P. Periodontitis and arterial stiffness: a systematic review and meta-analysis. J Clin Periodontol. 2015;42(11):977–87.
22. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. Atherosclerosis. 2014;236(1):39–46.
23. Teeuw WJ, Slot DE, Susanto H, Gerdes VE, Abbas F, D'Aiuto F, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. J Clin Periodontol. 2014;41(1):70–9.

24. Leira Y, Rodriguez-Yanez M, Arias S, Lopez-Dequidt I, Campos F, Sobrino T, et al. Periodontitis as a risk indicator and predictor of poor outcome for lacunar infarct. J Clin Periodontol. 2019;46(1):20–30.
25. Cowan LT, Lakshminarayan K, Lutsey PL, Folsom AR, Beck J, Offenbacher S et al. Periodontal disease and incident venous thromboembolism: the Atherosclerosis Risk in Communities study. J Clin Periodontol. 2018.
26. Daalderop LA, Wieland BV, Tomsin K, Reyes L, Kramer BW, Vanterpool SF, et al. Periodontal disease and pregnancy outcomes: overview of systematic reviews. JDR Clin Trans Res. 2018;3(1):10–27.
27. Iheozor-Ejiofor Z, Middleton P, Esposito M, Glenny AM. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. Cochrane Database Syst Rev. 2017;6:CD005297.
28. Nascimento GG, Leite FR, Do LG, Peres KG, Correa MB, Demarco FF, et al. Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis. J Clin Periodontol. 2015;42(6):495–505.
29. Gaio EJ, Haas AN, Rosing CK, Oppermann RV, Albandar JM, Susin C. Effect of obesity on periodontal attachment loss progression: a 5-year population-based prospective study. J Clin Periodontol. 2016;43(7):557–65.
30. Nascimento GG, Peres MA, Mittinty MN, Peres KG, Do LG, Horta BL, et al. Diet-induced overweight and obesity and periodontitis risk: an application of the parametric G-formula in the 1982 Pelotas birth cohort. Am J Epidemiol. 2017;185(6):442–51.
31. Shungin D, Cornelis MC, Divaris K, Holtfreter B, Shaffer JR, Yu YH, et al. Using genetics to test the causal relationship of total adiposity and periodontitis: Mendelian randomization analyses in the Gene-Lifestyle Interactions and Dental Endpoints (GLIDE) Consortium. Int J Epidemiol. 2015;44(2):638–50.
32. Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN, Battino M. Metabolic syndrome and periodontitis: is oxidative stress a common link? J Dent Res. 2009;88(6):503–18.
33. Kaye EK, Chen N, Cabral HJ, Vokonas P, Garcia RI. Metabolic syndrome and periodontal disease progression in men. J Dent Res. 2016;95(7):822–8.
34. Nascimento GG, Leite FRM, Peres KG, Demarco FF, Correa MB, Peres MA. Metabolic syndrome and periodontitis: a structural equation modeling approach. J Periodontol. 2018.
35. de Las Heras Gala T, Herder C, Rutters F, Carstensen-Kirberg M, Huth C, Stehouwer CDA, et al. Association of changes in inflammation with variation in glycaemia, insulin resistance and secretion based on the KORA study. Diabetes Metab Res Rev. 2018;34(8):e3063.
36. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, et al. Periodontitis and diabetes: a two-way relationship. Diabetologia. 2012;55(1):21–31.
37. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, et al. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev. 2015;(11):CD004714.
38. Leite FRM, Nascimento GG, Baake S, Pedersen LD, Scheutz F, Lopez R. Impact of smoking cessation on periodontitis: a systematic review and meta-analysis of prospective longitudinal observational and interventional studies. Nicotine Tob Res. 2018.
39. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol. 2018;6(12):954–65.
40. Kocher T, Konig J, Borgnakke WS, Pink C, Meisel P. Periodontal complications of hyperglycemia/diabetes mellitus: epidemiologic complexity and clinical challenge. Periodontol 2000. 2018;78(1):59–97.
41. Leite FRM, Peres KG, Do LG, Demarco FF, Peres MAA. Prediction of periodontitis occurrence: influence of classification and sociodemographic and general health information. J Periodontol. 2017;88(8):731–43.
42. Billings M, Holtfreter B, Papapanou PN, Mitnik GL, Kocher T, Dye BA. Age-dependent distribution of periodontitis in two countries: findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012. J Periodontol. 2018;89 Suppl 1:S140–S58.

Dental Health Services Epidemiology

David Brennan

Contents

26.1 Introduction – 396

26.2 Defining Health Services Research – 396

26.3 Conceptual Models of Health Services Research – 397

26.4 Use of Health Services – 397

26.5 Types of Health Services Research – 398

26.6 Dental Visits – 398
26.6.1 Inequalities as a Focus of Health Services Research into Visits – 399
26.6.2 Predisposing-Enabling-Need Model as a Framework for Dental Visits – 400
26.6.3 Check-Up Visits – 400
26.6.4 Problem-Based Visits – 401
26.6.5 Favourable Visit Patterns – 401
26.6.6 Expenditure on Care/Visits as an Outcome – 401

26.7 Dental Services – 402
26.7.1 Changes in Dental Services – 402
26.7.2 Relative Value Units – 403
26.7.3 Applications of Dental Services Research – 403
26.7.4 Linking Services to Outcomes – 404

26.8 Conclusion – 405

References – 405

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_26

26

Learning Objectives

- To define health services research
- To recognise conceptual models of health services research
- To understand research into dental visiting and dental services

26.1 Introduction

Dental health services research builds on concepts and the body of research from the general field of health services research. According to Scott and Campbell [1], health services research has the potential rival biomedical research in importance to the advancement of clinical practice and the population.

Health services research has been expressed as examinations of the question of what actually happens in the delivery of care. This is the examination of the outcomes of dental public health activity and, in particular, the outcomes measured in terms of oral health [2].

As an example of a key issue in dental health services research, Sheiham [3] questioned the evidence regarding the scientific basis for six-monthly dental examinations. In 1992, Bader [4] reported that appropriateness of care was an issue for dentistry, as many common dental treatments were not supported by research evidence. A systematic review of the effectiveness of routine dental checks in adults and children found that there was no existing high-quality evidence [5]. A Cochrane review concluded that there was insufficient evidence from randomised clinical trials to support or refute six-monthly recall intervals [6]. Similarly, another systematic review concluded that the evidence on recall intervals was weak and not strong enough to support a specific recall interval protocol for all patients [7]. Scale and clean services are another commonly provided dental service. However, a Cochrane review found that there is insufficient evidence to determine the effects of routine scale and polish treatments [8]. Results from a randomised clinical trial of single-visit scale and polish in patients with no significant periodontal disease found no differences in oral hygiene outcomes and concluded that larger trials with more comprehensive measurement and follow-up were needed [9]. These issues in dental health service research have important applications for evidence-based dentistry.

As noted by Coulter [10], there are significant gaps in the pursuit of evidence-based practice in dentistry that can be identified by examining health services research and dentistry. One gap is that between the existing evidence for the effectiveness of dental therapy and the actual practice. There is also a gap between existing evidence and the evidence required to claim that dentistry is actually evidence-based. Such evidence-based practice needs effectiveness studies that reflect real-world situations. It is possible that interventions or services could have similar efficacy, but vary in their effectiveness. There is a need to study outcomes and effectiveness to improve the quality of care and ultimately to provide better patient outcomes [10].

26.2 Defining Health Services Research

While there are a number of definitions of health services research, the Institute of Medicine of the National Academy of Sciences suggested a definition in 1979 that related to research into the structure, process and effects of health services. It was later updated in 1995 to include the multidisciplinary nature of such research and to acknowledge more specifically research into fields such as costs, quality and outcomes of services, as well as access to services and their organisation and delivery. The updated definition put more emphasis on the multidisciplinary nature of the field, the range of research from basic to applied, and the effects of health services on both individuals and populations [11]. Such newer definitions acknowledged that health services research is concerned with a broader continuum of health services focusing on population-based, as well as personal services; and that it incorporates aspects that involve the accountability of the system for ultimately improving the health of populations, as well as individuals [12].

This expanded view of health services research moves from a focus on individual patient–clinician encounters to include community and environmental contexts. This acknowledges the context in which encounters occur and also give importance to the roles of other medical and non-medical factors that can influence individual and population health. This view enables health outcomes to be evaluated at micro or macro levels – the micro level being a clinical perspective for individual patients and the macro level being a population perspective of health determinants [12].

In 2000, the Association for Health Services Research (AHSR) definition of the field of health services research also noted the multidisciplinary aspect of health services research and the importance of such research for health and well-being. This definition broadened the scope of health services research to include personal behaviours and social factors. Personal behaviours can include aspects such as smoking, use of seat belts and diet. Social factors comprise aspects such as income, education and occupation. The broadening of scope acknowledges the role of families, organisations, institutions and communities on health services and health outcomes [11].

26.3 Conceptual Models of Health Services Research

Donabedian proposed using the terms structure, process and outcome to evaluate the quality of healthcare. Broadly, 'structure' was defined as the settings, qualifications of providers and administrative systems through which care takes place; 'process' was defined as the components of care delivered; and 'outcome' was defined in terms of recovery, restoration of function and survival [13].

Structure refers to the attributes of the settings in which care takes place. This includes material resources such as facilities, equipment and finance; human resources such as the number and type of personnel; and organisational structure such as staff organisation and methods of reimbursement. Process refers to what is actually done in the delivery of healthcare. It includes the activities in seeking care by the patient, the provision of care and the activities of the provider in terms of diagnosis and recommending or implementing healthcare. Outcome refers to the effects of care on the health status of patients and populations [14].

This approach to quality assessment is used as better structural aspects of care increases the chances of good process, and good process aspects of care increases the probability of a good outcome. Structural characteristics are considered a blunt instrument in quality assessment, but should be a major aspect of system design. Neither the measurement of process nor the measurement of outcome is considered as inherently superior in this framework, since there is a postulated linkage between them. Outcomes can be delayed and difficult to obtain if they occur after completion of care. Outcomes are considered to have the advantage of reflecting all contributions to care. However, it may not be possible to know what goes wrong with adverse outcomes unless the process is documented [14].

The concepts of structure, process and outcome were built on by Starfield [15] in a health services research conceptual model that comprised four determinants of health. These comprised the genetic composition of patients, patient behaviour, the practice and environment. Clinical practice includes structural components such as staff, facilities, organisation and financing, as well functional components such as diagnosis and provision of care. Provision of care includes the interaction of functional aspects with the behaviour of patients [15].

A framework was further developed to bridge and integrate health services and public health research [12]. In this framework, structure refers to the availability, organisation and financing of healthcare programmes, the nature of the populations served by healthcare systems, and the physical, social and economic aspects of their environment. Process covers the relationships of patients and providers in the delivery of care, as well other environmental and behavioural influences on health risks. Clinical effectiveness relates to the impact of healthcare on improvements in health for individual patients. Production efficiency is the combination of inputs needed to produce services at the lowest costs. Procedural equity relates to the fairness of the delivery of care. Clinical effectiveness, production efficiency and procedural equity focus on improvements in the health of individuals at the micro level.

At the macro level, population effectiveness, allocative efficiency and substantive equity focus on community-wide health improvements. Population effectiveness relates to the role of healthcare and other factors on the health of populations. Allocative efficiency addresses the combination of inputs to produce the greatest health improvements, given available resources. Substantive equity is judged by how equally health benefits are shared across groups in the community. Effectiveness, efficiency and equity are viewed as intermediate healthcare outcomes that are ultimately linked to the health of individuals and communities.

26.4 Use of Health Services

The Behavioural Model of Health Services is a key model used to understand how people access and utilise health services [16]. This model divided factors related to health service use into predisposing, enabling and need. Predisposing characteristics include demographics such as age and sex. Social structure often includes elements such as education, occupation and ethnicity. Health beliefs span the range of health-related attitudes, values and knowledge that can shape perceptions of need and use of health services. Enabling resources can include both community level and personal resources. Community resources include availability of healthcare providers and facilities required to conduct health services. Personal resources cover aspects such as income, insurance and travel. Need variables can be considered as either perceived or evaluated. Perceived need may reflect social structure and incorporate social context and health beliefs as well as considerations of disease. Evaluated need is more biological, reflecting professional judgement in relation to health status.

Since the inception of the model, there have been subsequent refinements to the original Behavioural Model of Health Services [16]. Some of these included expansion of the measures of use of health services to include aspects such as types and sites of services. In addition, consumer satisfaction was introduced into the model as an outcome of health service provision, along with perceived and evaluated health status as outcomes.

The Behavioural Model has tended to be classified as a predictive model, with an emphasis on variance explained by the model. Other models [17] can be considered more as process models that have more emphasis on sociocultural and psychosocial factors. A model of the dental care process emerged from issues in applying these models to dental care to achieve a more comprehensive view that moved beyond descriptive models and adopted more multidisciplinary approaches [18].

The dental care process model has some key features of note. The notion of an episode of dental care reflects how dentistry is delivered with services provided within visits, and potentially multiple visits comprising a course of care that reflects the diagnosis and treatment plan. The nodes in the pathway correlate with variables in the process of dental care. These variables include the probability of beginning an episode of dental care for all individuals. For those individuals who commence an episode of care, the variables include clinical oral health status and treatment needs from the provider examination and diagnosis, number and cost of services in the treatment plan, probability of completing treatment, and the eventual number, cost and quality of services provided. Outcomes of the episode of care fall into diagnostic, therapeutic and educational. Diagnostic outcomes are reflected in the number and cost of services in the treatment plan. Therapeutic outcomes include the determination of whether the needs of the patient were satisfied, the change in the perceived and clinical oral health status related to the services provided, and the quality of life aspects related to the episode of care. Educational outcomes can include knowledge, attitudes and behaviour such as health information, satisfaction with care and self-care changes resulting from the episode of care.

26.5 Types of Health Services Research

In looking at the types of health services research, studies of health services research can span a range of broad fields. These include effectiveness and appropriateness of care studies that include effectiveness research, implementation research and appropriateness research. Other areas include clinical practice performance, assessing access to indicated care, assessing outcomes of care and patient preferences, deciding allocation of resources and evaluating effects of organisational restructuring [1].

Effectiveness and appropriateness of care: Effectiveness research asks, 'What is the right thing to do?' or 'What type of care produces health benefits in a particular clinical situation?' While randomised clinical trials are recommended, they are often not feasible. In such cases, observational studies and quasi-experimental methods may be performed. Such observational studies can provide estimates of effectiveness in real-world circumstances. Appropriateness research asks, 'Was the most appropriate thing done given the clinical circumstances?' This covers issues of overuse, underuse or misuse of interventions. As such, findings of appropriateness studies may identify potential problem areas.

Clinical practice performance: Performance research asks, 'Was the right thing done well?' Issues include timely access to care, efficient care delivery, issues of safety and technical quality.

Assessing access to indicated care: This can involve underuse of indicated interventions or overuse. Health services research can identify where patients are denied indicated care on the basis of characteristics, such as ethnicity, gender and socio-economic status.

Assessing outcomes of care and patient preferences: Outcomes research asks, 'Was the outcome of care satisfactory from both the clinician's and patient's point of view?' Emphasis in this research is given to patient-based outcomes that assess the effects of care on quality of life and level of satisfaction with care received. Such research also seeks to determine if current practice is consistent with preferences of patients and if it is producing the outcomes that are desired by patients.

Deciding allocation of resources: This type of research is directed at deciding how to use limited resources when managing various diseases and conditions. This requires an evaluation of disease prevalence, the costs of care (direct and indirect), probabilities of outcomes for specific interventions and valuation of specific outcomes from a patient or societal point of view.

Evaluating effects of organisational restructuring: Changes such as regionalisation, corporatisation, privatisation, downsizing and outsourcing of health services may impact on health services. There is a need for research into how these changes impact on quality of care and patient outcomes.

26.6 Dental Visits

Much of dental health services research is directed at studies of dental visiting. Typically, such studies have focussed on access to dental care or on number of dental visits utilised. Among studies of access to dental care, a commonly used approach is to focus on whether one or more dental services were demanded during the last year. Studies of dental utilisation have often focussed on the number of dental visits received among those who had made a dental visit in the last year.

The study by Grytten [19] provides an example of a study of accessibility to dental care using demand for one or more visits in the last year as the main outcome of interest. The overall aim of the study was to

examine how income influenced the demand for dental services in Norway, and whether this had changed over time. Family income was the main independent variable. Other variables such as education, age, gender, population-to-dentist ratio and number of teeth were included as control variables. Data from personal interviews were used from three independent samples that were representative of the Norwegian population aged 20 years and older. Demand, defined as whether or not an individual had visited the dentist in the last year, was the main outcome (coded as 1 if demanded dental services, otherwise coded as 0 for analysis). Analysis was conducted using logistic regression with odds ratios as the effect measure. The findings showed that inequalities in use of dental services among different income groups had decreased over the observation period of the study.

Some studies report on dental visiting, but based on time intervals other than the last year. For example, a study of use of dental care among older adults in Brazil used whether a dental visit had been made in the past 2 years as the outcome variable [20]. Independent variables included demographic, oral health and socio-economic characteristics.

The number of visits has also been frequently used as an outcome of dental health services research. Mueller and Monheit [21] used data from the US National Medical Care Expenditure Survey to study the effects of insurance on demand by a standard population of white adults aged 16–64 years. In a two-part model, demand was measured by access to care and by amount of services provided conditional on some use of dental care. That is, access is first modelled by whether or not a dental visit was made, and then in the second part, the amount of use is measured through the number of dental visits made by those who made dental visits during the survey year. Insurance was the main explanatory variable, with other variables included to control for differences in ability to pay, preferences and health status. Findings indicated that the primary effects of dental insurance were to facilitate access to care and to increase dental expenditures.

In another example of the use of two-part models to investigate socio-economic demand for dental visits, Petersen and Pedersen [22] used a survey of Danish employees. Number of dental visits per year was the main dependent variable, along with dental status measured as the number of teeth. Other variables included previous use of dental care, expectations about avoiding losing teeth, time costs related to the use of dental care, income and price. Structural equations were estimated using multiple regression analysis by two-stage least-squares method. They found that dental visits were influenced by dental health status, expectations regarding value of dental care, income and price of dental care.

26.6.1 Inequalities as a Focus of Health Services Research into Visits

Inequality in healthcare services, including services for dental care, is considered to play a role in creating health inequalities [23]. Many of these studies assess use of dental services by income. For example, a study of trends in dental care use in the United States used data from the National Health Interview Survey [24]. The main outcome variable was whether any dental visits were made in the past year. Data were available for both children and adults. Information on income was expressed in terms of poverty status, using the ratio of the family's income to the Federal Poverty Level thresholds. This controls for the size of the family and the age of the head of the household. Gradients in use of dental services by poverty levels were evident for both children and adults.

A study by Listl [25] approached income-related inequalities in dental service use by means of Concentration Indices and Slope Indices of Inequality to capture relative and absolute inequality. Data were used from adults aged 50 years or older from 14 different European countries. Incidence of any dental treatment was presented by equalised net monthly income. The income scale accounts for household size and age of household members. A disproportionate concentration of access to treatment was identified among the richer populations in all 14 countries.

While many studies of socio-economic inequality in use of dental care have been based on income, other studies have used education as an indicator of socio-economic status. Macek et al. [26] used data from nationally representative US health surveys to examine dental visits among adults. Dental visits in the last year were examined by education, along with age, gender, race and poverty status. Education status was based on the number of years of formal education. Gradients in dental visiting by level of education were observed consistently across all surveys.

A study of health-related behaviours and socio-economic disparities in a nationally representative sample of US adults included education as an explanatory variable and dental visits as an outcome [27]. Years of education was categorised into three groups: less than 12 years, 12 years and more than 12 years. Other variables included poverty-income ratio, age, sex, ethnicity and dental insurance. Dental visiting exhibited a clear gradient by both education and income.

A study from Norway examined socio-economic inequalities in dental utilisation among adults aged 20 years or older [28] with a focus on both income and education. Use of dental services was measured by whether a dental visit had been made in the previous

12 months. Disposable income per equivalent adult was determined using household income after tax, while education level was the highest level attained. Income-related horizontal inequity was estimated by means of concentration indices. Education-related inequity was estimated as relative risks. Their findings revealed pro-rich and pro-educated inequity in use of dental care.

Kailembo et al. [29] examined wealth as a predictor of use of dental services in a national US survey of adults aged 20 years and older. The objective of the study was to assess how two socio-economic status measures, income and wealth, compare in relation to socio-economic disparity in dentist visits. The dependent variable was not having a dentist visit in the past 12 months. The income variable used the poverty income ratio calculated by dividing family income to the poverty level threshold for family size and survey year. The wealth variable used a combination of family income and home ownership variables. Wealth was used as a socio-economic variable in addition to income as income in combination with assets such as housing may better predict health than income alone. Covariates included socio-demographic factors and untreated dental caries. They found that lower socio-economic positions (wealth or income) were associated with not having dentist visits, but the socio-economic patterning varied by factors such as age and ethnicity.

26.6.2 Predisposing-Enabling-Need Model as a Framework for Dental Visits

Many reports of use of dental visits have adopted the behavioural model framework of Andersen [30]. A study of use of oral healthcare in Finland was based on nationally representative surveys of adults aged 30 years or older [31]. The outcome variable used in the study comprised the use of oral healthcare services in the previous year. Predisposing variables comprised sex and age group; enabling variables were education, recall, dental fear, use of services, household income and barriers to care; and need variables included perceived need, self-rated oral health and denture status. Being a regular dental attender was a key determinant for visited a dentist in the previous year. Both organisational and individual enabling factors were prominent in service utilisation particularly in the private sector.

Kiyak [32] used the behavioural model to examine the effect of attitudes as predisposing factors. This was examined in a study of older persons that compared users of low-cost dental services with comparable older adults that had not used dental care. Predisposing factors included aspects such as age, sex, education and occupation. Enabling factors included income and insurance. Need included number of teeth, dentures and perceived need. Additional predisposing variables included social network and a series of beliefs about oral healthcare and ratings of their importance. Attitudes were found to be the best predictors of the decision to seek dental care. However, a combination of predisposing, enabling and need variables explained the most variance.

While many studies have adopted the Andersen behavioural model as a framework, there is a lack of studies that explicitly test the model in relation to oral health. However, a study by Baker [33] examined the direct and mediated pathways between social, attitudinal and behavioural factors and perceived oral health outcomes. A two-stage structural equation model process was tested using a general population sample from the UK adult dental health survey. Overall, the findings provided support for the behavioural model as applied to perceived oral health. Enabling resources predicted need, while enabling resources and need predicted personal health practices and use of services, which predicted perceived oral health quality of life.

Manski and Moeller [34] provided a concise review of barriers to oral health for older adults in Europe and the United States using the categories of predisposing, enabling and need factors. In doing so, they further class these into modifiable and non-modifiable groupings. Here, for example, age and sex are considered as non-modifiable predisposing factors while dental anxiety could be considered a potentially modifiable predisposing factor in relation to use of dental care. Predisposing, enabling and need factors such as low income, less education and poor health were found to have incremental effects in combination as multiple barriers to access to dental care.

26.6.3 Check-Up Visits

More frequent dental visits may reduce tooth loss and help to maintain function [35]. Regular dental attendance within a 2-year period has also been linked to better oral health in terms of impacts of dental health problems [36]. In addition to the analysis of dental visits in terms of their frequency, there is also interest in analysing the type of dental visit. A major focus of type of dental visit is the dental check-up. Kino et al. [37] examine whether public expenditure on health was associated with dental check-ups in European countries. The outcome of dental check-ups comprised dental visits for an oral examination and getting advice on oral health in the last 12 months. Public expenditure on health was defined as a percentage of gross domestic product (GDP), which was a contextual factor. Individual factors included age, gender, marital status, urbanisation, education, subjective social status and difficulty in paying bills. Multilevel logistic regression models were used

to examine the association between dental check-ups and healthcare expenditure adjusted for demographic factors, GDP and socio-economic status. The findings showed that greater support for healthcare and better healthcare systems were positively associated with routine dental attendance.

26.6.4 Problem-Based Visits

In contrast to a focus on check-up visits, there is also interest in examining visiting for dental problems or relief of pain as a potential risk indicator for poor access and worse oral health status. Riley et al. [38] reported that poorer overall oral health was associated with visits due to pain. People who attend for dental visits who are experiencing pain are likely to have more advanced disease, and so they have more limited treatment options [39]. A study by Roberts-Thomson et al. [40] based on the Australian National Survey of Adult Oral Health examined use of dental services using whether the reason for visit was for relief of pain within the last 2 years as the outcome variable. Explanatory variables consisted of age, sex, country of birth, highest level of educational qualifications, occupation and income. Logistic regression models showed that odds of visiting for relief of pain varied by age, country of birth, education and income.

A study by Luzzi et al. [41] looked at changes over time in problem-based dental visiting in Australia. The trend in the percentage of persons usually visiting the dentist for a problem was analysed using a standard cohort table and a set of nested age–period–cohort models. Usually visiting the dentist for a problem was used as the outcome variable. Usual reason for visiting the dentist was adopted, as it reflects intention and longer-term dental visiting patterns. This study found similar, consistent patterns in the age–period and age–cohort models, with usually visiting for a problem tending to be higher in older age groups and older cohorts. However, usually visiting for a problem tended to decline over time for most age groups and most age cohorts.

26.6.5 Favourable Visit Patterns

Dental visiting has been classified into problem-oriented attenders and regular attenders [42]. Problem-oriented attenders tend to seek care when they have a specific problem, while regular attenders seek care regardless of whether they have a problem. Problem-oriented attenders may be characterised by more negative attitudes to both oral health and dental care. Dental visiting patterns may be considered as either favourable or unfavourable. Those with favourable dental attendance patterns tend to have a usual dental care provider that they visit at least once a year for a dental check-up. In contrast, unfavourable dental attendance patterns correspond to visiting the dentist infrequently and usually for dental problems. Ellershaw and Spencer [43] found that among dentate Australian adults from a national survey, 40% were classified as having a favourable pattern of dental attendance, while 29% were classified in the unfavourable attendance group. Being in the unfavourable visit pattern group was associated with being uninsured, lower income, unemployment, lower educational attainment and living in disadvantaged areas. Unfavourable dental attendance was also associated with poorer oral health self-ratings, more experience of toothache, gum disease and food avoidance.

While these data on favourable visit patterns are from cross-sectional information, there are reports on longer-term findings from cohort studies. For example, Thomson et al. [44] reported on long-term dental visiting patterns and adult oral health. In a prospective cohort study from New Zealand, the use of dental services was collected at ages 15, 18, 26 and 32. Routine dental attenders were classified as those who usually attended for a check-up and had made a dental visit in the last 12 months. Oral health outcomes included dental caries, missing teeth and self-rated oral health. Covariates included sex and socio-economic status. Models were fitted using generalised estimating equations. The findings showed that by the age of 32 years, routine attenders had better self-reported oral health and less tooth loss and caries.

Astrom et al. [45] reported on the effect of long-term routine dental attendance on the oral health of Swedish adults from middle-aged to older age from a prospective study. In this study, routine dental attendance comprised attending a dentist in the previous year for dental check-ups from 50 to 65 years of age. The study assessed the association of long-term routine dental attendance with oral health-related quality of life and major tooth loss controlling for social factors and the type of treatment sector utilised. The findings showed that while routine attendance decreased from age 50 to 65 years, long-term routine attendance had positive effect on quality of life and tooth loss. These findings indicated some support for the benefit of routine dental attendance for preventive check-ups in older adults.

26.6.6 Expenditure on Care/Visits as an Outcome

In a study of demand/utilisation in relation to income, Grytten and Holst [46] use two data sets representative of the Norwegian population aged 20 years and older. They measured demand in terms of whether or not a

person had visited a dentist in the previous year. They also measured utilisation as the expenditure on dental services during the previous year among those who had made any dental visits. Demand was analysed using logistic regression and utilisation with ordinary least-squares regression. Family income was the main explanatory variable, with number of individuals in the family, gender and dentist density as control variables. Their main finding was that the increase in demand with an increase in income was less for young adults than for older adults.

A variation on using expenditure for dental visits as an outcome is to focus on avoiding or delaying dental care due to cost. If the cost of dental care acts as a barrier to a pattern of regular dental attendance, then this could impact on the timeliness and comprehensiveness of the care. Chrisopoulos et al. [47] explored the extent to which age, period and cohort factors contributed to avoiding or delaying visiting a dentist because of the cost. Data were used from four national dental telephone interview surveys of Australian residents aged 5 years and over. Financial barriers to dental care were assessed using the question 'During the last 12 months, have you avoided or delayed visiting a dental professional because of the cost?', to which respondents answered 'yes' or 'no'. The age–period–cohort analyses were adjusted for sex and household income. They reported an overall increase in the proportion of people avoiding or delaying visiting a dentist indicating the presence of period effects.

26.7 Dental Services

In an episode of dental care, treatment items or dental services are provided by a service provider to a patient at one or more visits that comprise the treatment plan. Dental services are often classified into main areas of service. For example, examinations and radiographs are classified as diagnostic, dental prophylaxis and fluoride applications as preventive, and fillings as restorative services. So, services may be reported at a service item level such as radiographs or at a service area level such as diagnostic. Services may be presented as percentage of persons receiving one or more services or as mean number of services. Services can be presented at different units, such as services per visit or services per year.

While much of dental health services research has focussed on dental visits in terms of access, studies that look at the types of services provided give a fuller picture of what actually happens during a dental visit or series of visits that make up an episode of dental care. A fundamental application of service provision research is to provide basic descriptive data on types of services, usually broken down by some key indicator variables. Manski et al. [48] presented a study that described dental procedures provided to children and adolescents in the United States by poverty status and insurance coverage using data from the Medical Expenditure Panel Survey. The primary outcome variable represented the types of dental procedures that were received during dental visits in the last year. Overall, the findings showed that diagnostic (41.2%) and preventive (35.8%) services accounted for most of the dental care received by children up to 20 years of age, while restorative procedures accounted for just 5% of the total. Using a similar approach, it was also found that diagnostic and preventive procedures accounted for over 75% of all dental services received by working-age adults [49]. Other studies have reported on service patterns of dental providers other than dentists. For example, proportions of services such as fluoride applications and fissure sealants varied between oral health therapists, dental therapists and dental hygienists [50], along with numbers of services per patient [51].

26.7.1 Changes in Dental Services

In addition to providing basic descriptive data on types of services, another application of service provision analyses is to provide information on trends in service mix over time. Sequential cross-sectional comparisons have been used to demonstrate how the pattern of dental services has changed over time. An understanding of changes in treatment patterns can be applied to workforce planning in terms of expected future needs for treatment. Patterns of clinical dental care can reflect the patterns of diseases and conditions within the population and the age structure of that population [52]. The diagnosis and treatment plan emanating from the clinical oral health status can be reflected in characteristic patterns of dental services [39]. A study of trends in dental treatment used data from dental insurance claims in the United States. The number of each type of service was divided by the number of patients who were treated to estimate annual per capita use of dental services [53]. They found that over time the number of restorative procedures declined, as did the number of prosthodontic procedures. However, the use of implants increased over time. A long-term study of Australian dentists was used to analyse trends in dental services over time [54]. Results were reported on rates of service provision per visit between 1983 and 2010. The findings showed that the profile of services provided by dentists had changed over time to include less emphasis on replacement of teeth and more focus on the diagnosis, prevention and retention of natural dentitions.

In studying changes in dental services over time, other approaches can be adopted, such as age–period–cohort analyses [55]. For example, Ju et al. [56] reported on age, period and cohort factors of dentists in relation

to diagnostic, preventive and total dental services over time in Australia. Time trends in the mean rates of the services were described using a standard cohort table, and negative binomial regression was applied to estimate age, period and cohort effects. Findings showed an increasing rate of diagnostic, preventive and the total services when moving from older to younger cohorts among Australian dentists that suggested a sustained shift towards these services into the future.

In addition to age–period–cohort analyses based on a synthetic cohort approach, longitudinal analyses can be used to assess changes in dental service provision over time. Ju et al. [57] calculated the mean proportion of dental services from practitioner activity logs and used mixed effects regression models to estimate longitudinal change in the proportion of services provided by dentists. Among the findings, they reported that provision of restorative and oral surgery services, as a proportion of all services provided, was declining.

26.7.2 Relative Value Units

In reporting dental services and changes over time, it can be useful to convert the broad range of different service types to a common scale. Relative value units have been developed for this purpose [58]. Relative value units have application in health financing as a payment mechanism and practice management tool [59], and they can be applied to cost analysis and to benchmarking. Relative value units can be employed as objective productivity measures and can inform fee setting. Responsibility loadings used to calculate relative value units have been related to aspects such as knowledge, skill and also the clinical and technical risk associated with a particular type of service [60]. Time and knowledge have been suggested as important considerations in the process of determining values of dental services [61].

The relative value unit approach tends to use a defined base service such as an occlusal amalgam restoration that is assigned a responsibility loading of 1.0. Then, other services are valued in relation to this service as a reference point. Additional factors are required to convert relative value units into monetary values using laboratory costs, office overheads and cost of materials [60]. In establishing a common scale of work effort, there have been a range of approaches. The Swedish Dental Service Unit was based on direct time studies of dental treatments [62]. Other approaches to valuing types of dental procedures include relative time-cost units that were based on personnel costs, task mixes and task times involved in dental procedures [63]. Studies using time units are limited by the restriction of using time as the only measure of relative value of services, without accounting for other factors such as responsibility associated with service provision. A set of values for dental items was published in the United States [64] and, since then, a set has been published from a sample of Australian dentists [65, 66].

26.7.3 Applications of Dental Services Research

Research into the restoration cycle provides an example of the value of dental health services research. As noted by Elderton [67], 'it cannot be assumed that dentistry, as widely practised, is necessarily good for the teeth'. A study of the operative treatment provided to dentate adults from Scotland over a 5-year period showed that patients who attended a dentist more often had more restorations in proportion to the episodes of care provided [68]. They found that more restorations were associated with greater likelihood of more in the future and that replacement restorations increased as the total number of restorations increased. This pattern reflects the repeat restoration cycle [67], whereby dentists place and replace restorations with a weakening of the teeth in the process.

A current direction in dental care is a move towards a more minimally invasive approach. This approach presents a treatment philosophy that has an emphasis on conservation of healthy tooth structure so that the restoration and re-restoration cycle can be avoided [69]. However, previous reports of dental services by caries lesion severity had suggested that treatment patterns were not consistent with minimum intervention [70]. There have also been reports that there is a persistent belief among dentists that questionable and early carious lesions be restored even though preventive measures could potentially reduce future caries recurrence [71]. A further study of treatment provided to patients with a main diagnosis of coronal caries was conducted to assess whether treatment patterns were consistent with minimum intervention [72]. It was found that the treatment of coronal caries was characterised by high rates of restorative care. Gross lesions had lower restorative rates, but higher rates of endodontic and extraction services. However, there was little differentiation in the treatment provided for coronal caries between initial and cavitated lesions. This lack of differentiation suggested that there is scope for increased management of initial carious lesions by the adoption of more minimum intervention approaches.

Another area of research in dental health services relates to variations in service rates. Variation in service provision has been noted in medicine and dentistry [73–75], with such variation a potential issue in relation to appropriateness of care [4]. Factors pertaining to dentists have been suggested as possible sources of variation. These dentist factors include practice beliefs

[76], clinical decision making (i.e., diagnosis or detection, decision to intervene and selection of treatment) and the interaction between dentists and patients [77]. Variation in service rates may also be associated with practice characteristics, for example, the size and busyness of practices [78] and practice age [76]. Area-based factors such as geographic location have been associated with variation in services [79]. Factors measured at the patient level that have been associated with service patterns include age and sex of the patient [74, 80], the insurance status of the patient [81], and reason for visit such as emergency visits [82]. Patient-level factors that include non-emergency visits, dental insurance and socio-economic status have been related to dental service rates, controlling for oral health status [83]. A study which provided a comprehensive model of dental service rates found that services were influenced by a large number of small effects from a wide range of dentist, practice and patient factors [84]. Similarly, a US study found that while general dentists provide a comprehensive range of services, provision was related to a broad range of dentist, practice and patient factors [85].

Networks of dentists can be applied to dental health services research using a dental practice-based research network as a platform to investigate a range of different research questions. For example, Gordan et al. [86] reported a cross-sectional study that quantified reasons why dentists repair or replace restorations. They found that dentists were more likely to replace than repair restorations. Factors associated with being more likely to repair restorations included recent graduation, being in a large practice, having placed the original restoration and involving fewer tooth surfaces. In another application of the dentist practice network, McCracken et al. [87] examined factors related to restoration longevity. Using a cohort design, they found that patient's age, a higher number of surfaces restored at baseline, the dentist's sex and the practice workload were predictive of restoration failure. However, restorative material and tooth type were not associated with longevity of restorations. Heaven et al. [88] reported on another application of the dentist practice network to quantify the level of agreement between dentists on treatment decisions. Using hypothetical clinical scenarios, they investigated the likelihood of later restorations for primary caries. They reported that dentists who recommended repair rather than replacement of existing restorations were significantly more likely to recommend later treatment of primary caries. They concluded that individual dentists exhibited consistency in treatment of primary caries and existing restorations, but found substantial variation between dentists.

26.7.4 Linking Services to Outcomes

An important aspect of dental services is to demonstrate a positive influence on health outcomes. There is a need for longitudinal studies of dental service provision and outcomes. This is particularly so for patient-based outcomes that can reflect the perspective of the patient [89]. As noted by Fiske et al. [90], dental care is expected to contribute to quality of life. They measured categories of oral handicap in terms of functional impairment, comfort, self-image and social interaction before dental treatment as well as any benefit of the treatment. They found that while 75% benefited from treatment, one third of patients with compromised oral function before treatment still were compromised following treatment.

Petersen and Nortov [91] reported on changes in oral health, health behaviours and quality of life among older adults in Denmark 3 years following the introduction of a dental care programme. They found a decline over time in reported poor function of dentures and less embarrassment related to teeth. In another study of older adults, Locker [92] reported a longitudinal study of self-perceived change in oral health status and receipt of dental treatment over a 3-year period. Change in oral health was assessed by global transition judgements and change score from oral health indexes. The findings showed that more dental visits and services were associated with improved oral health. Those who improved also received a wider range of diagnostic, preventive and therapeutic services.

Fisher et al. [93] looked at the effectiveness of dental care in relation to recovery from quality-of-life decrements in groups with diseases such as dental caries and periodontal disease. Dental care was found to be effective in treating quality-of-life decrements. A study by Crocombe et al. [94] used a service use log book and 12-month follow-up to assess whether routine dental attendance improved oral health-related quality of life. The findings showed that there was a statistically significant interaction in change in oral health impact for dental attendance by residential location. A study of change in self-reported oral health in relation to use of dental services over time used global oral health transition statements to elicit changes in health over a 2-year period [95]. Worsening in oral health was associated with extractions and dentures and was inversely associated with visiting and preventive care. Improvement in oral health was associated with preventive care and was inversely associated with endodontic treatment.

26.8 Conclusion

With the growing emphasis on evidence-based healthcare, there will be ongoing need for high-quality dental health services research to underpin the provision of dental care. As noted by Coutler [10], without a health services research component, the current move towards evidence-based dentistry would be hindered. Major issues related to health services research include linking structure, process and outcome; assessing the quality of care provided; evaluating aspects such as access, cost, services and care utilisation; measuring need for healthcare; and assessing patient-based outcome measures, such as satisfaction with care and health-related quality of life, and research into the appropriateness of care. All these issues are of central importance to the application of evidence-based dentistry.

However, in moving forward with a research agenda in dental health services, we need to be able to convey evidence from research in a meaningful way. Lohr and Steinwachs [11] advise that we need to formulate simpler and more effective ways of communicating both the information and importance of health services research. This is particularly so for stakeholders such as the public and policy makers.

In undertaking further research in dental health services, it is important to understand the broader importance of this research to the health of populations. This includes understanding the extent to which the health of populations as a whole is improved and whether the benefits are shared equally by all groups within the population [12].

References

1. Scott I, Campbell D. Health services research: what is it and what does it offer? Intern Med J. 2002;32:91–9.
2. Bader J. Health services research in dental public health. J Public Health Dent. 1992;52:23–6.
3. Sheiham A. Is there a scientific basis for six-monthly dental examinations? Lancet. 1977;2:442–4.
4. Bader J. The emergence of appropriateness-of-care issues. J Dent. 1992;71:502–4.
5. Davenport CF, Elley KM, Fry-Smith A, Taylor-Weetman CL, Taylor RS. The effectiveness of routine dental checks: a systematic review of the evidence base. Br Dent J. 2003;195:87–98.
6. Beirne PV, Clarkson JE, Worthington HV. Recall intervals for oral health in primary care patients. Cochrane Database Syst Rev. 2007;(4):CD004346.
7. Patel S, Bay RC, Glick M. A systematic review of dental recall intervals and incidence of dental caries. J Am Dent Assoc. 2010;141:527–39.
8. Beirne P, Worthington HV, Clarkson JE. Routine scale and polish for periodontal health in adults. Cochrane Database Syst Rev. 2007;000(4):CD004625.
9. Jones CL, Milsom KM, Ratcliffe P, Wyllie A, Macfarlane TV, Tickle M. Clinical outcomes of single-visit oral prophylaxis: a practice-based randomised controlled trial. BMC Oral Health. 2011;11:35.
10. Coulter ID. Evidence-based dentistry and health services research: is one possible without the other? J Dent Educ. 2001;65:714–24.
11. Lohr KN, Steinwachs DM. Health services research: an evolving definition of the field. Health Serv Res. 2002;37:15–7.
12. Aday LA. Establishment of a conceptual base for health services research. J Health Serv Res Policy. 2001;6:183–5.
13. Ayanian JZ, Markel H. Donabedian's lasting framework for health care quality. N Engl J Med. 2016;375(3):205–7.
14. Donabedian A. The quality of care. How can it be assessed? JAMA. 1988;260:1743–8.
15. Starfield B. Health services research: a working model. N Engl J Med. 1973;289:132–6.
16. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav. 1995;36:1–10.
17. Mechanic D. Medical sociology. 2nd ed. New York: Free Press; 1978.
18. Grembowski D, Andersen RM, Chen M. A public health model of the dental care process. Med Care Res Rev. 1989;46:439–96.
19. Grytten J. Accessibility of Norwegian dental services according to family income from 1977 to 1989. Community Dent Oral Epidemiol. 1992;20:1–5.
20. Bof de Andrade F, Drumond Andrade FC, Noronha K. Measuring socioeconomic inequalities in the use of dental care services among older adults in Brazil. Community Dent Oral Epidemiol. 2017;45:559–66.
21. Mueller CD, Monheit AC. Insurance coverage and the demand for dental care. Results for non-aged white adults. J Health Econ. 1988;7:59–72.
22. Petersen PE, Pedersen KM. Socioeconomic demand model for dental visits. Community Dent Oral Epidemiol. 1984;12:361–5.
23. Wamala S, Merlo J, Bostrom G. Inequity in access to dental care services explains current socioeconomic disparities in oral health: the Swedish National Surveys of Public Health 2004-2005. J Epidemiol Community Health. 2006;60:1027–33.
24. Wall TP, Vujicic M, Nasseh K. Recent trends in the utilization of dental care in the United States. J Dent Educ. 2012;76:1020–7.
25. Listl S. Income-related inequalities in dental service utilization by Europeans aged 50+. J Dent Res. 2011;90:717–23.
26. Macek MD, Manski RJ, Vargas CM, Moeller J. Comparing oral health care utilization estimates in the United States across three nationally representative surveys. Health Serv Res. 2002;37:499–521.
27. Sabbah W, Tsakos G, Sheiham A, Watt RG. The role of health-related behaviors in the socioeconomic disparities in oral health. Soc Sci Med. 2009;68:298–303.
28. Vikum E, Krokstad S, Holst D, Westin S. Socioeconomic inequalities in dental services utilisation in a Norwegian county: the third Nord-Trøndelag Health Survey. Scand J Public Health. 2012;40:648–55.
29. Kailembo A, Quiñonez C, Lopez Mitnik GV, Weintraub JA, Williams JS, Preet R, Iafolla T, Dye BA. Income and wealth as correlates of socioeconomic disparity in dentist visits among adults aged 20 years and over in the United States, 2011–2014. BMC Oral Health. 2018;18:147.
30. Andersen RM. National health surveys and the behavioral model of health services use. Med Care. 2008;46:647–53.
31. Suominen A, Helminen S, Lahti S, Vehkalahti MK, Knuuttila M, Varsio S, Nordblad A. Use of oral health care services in Finnish adults – results from the cross-sectional Health 2000 and 2011 Surveys. BMC Oral Health. 2017;17:78.
32. Kiyak HA. An explanatory model of older persons' use of dental services. Implications for health policy. Med Care. 1987;25:936–52.

33. Baker SR. Applying Andersen's behavioural model to oral health: what are the contextual factors shaping perceived oral health outcomes? Community Dent Oral Epidemiol. 2009;37:485–94.
34. Manski RJ, Moeller J. Barriers to oral health across selected European countries and the USA. Int Dent J. 2017;67:133–8.
35. Sheiham A, Maizels J, Cushing A, Holmes J. Dental attendance and dental status. Community Dent Oral Epidemiol. 1985;13:304–9.
36. Richards W, Ameen J. The impact of attendance patterns on oral health in a general dental practice. Br Dent J. 2002;193:697–702.
37. Kino S, Bernabe E, Sabbah W. The role of healthcare system in dental check-ups in 27 European countries: multilevel analysis. J Public Health Dent. 2017;77:244–51.
38. Riley JL 3rd, Gilbert GH, Heft MW. Orofacial pain: patient satisfaction and delay of urgent care. Public Health Rep. 2005;120:140–9.
39. Brennan DS, Spencer AJ, Szuster FS. Service provision patterns by main diagnoses and characteristics of patients. Community Dent Oral Epidemiol. 2000;28:225–33.
40. Roberts-Thomson KF, Luzzi L, Brennan DS. Social inequality in use of dental services: relief of pain and extractions. Aust N Z J Public Health. 2008;32:443–8.
41. Luzzi L, Chrisopoulos S, Brennan DS. Decline in usually visiting the dentist for a problem in Australia, 1994 to 2010: an age–period–cohort analysis. Community Dent Oral Epidemiol. 2014;42:349–57.
42. Gilbert GH, Stoller EP, Duncan RP, Earls JL, Campbell AM. Dental self-care among dentate adults: contrasting problem oriented dental attenders and regular dental attenders. Spec Care Dentist. 2000;20:155–63.
43. Ellershaw AC, Spencer AJ. Dental attendance patterns and oral health status. Dental statistics and research series no. 57. Cat. no. DEN 208. Canberra: AIHW, 2011.
44. Thomson WM, Williams SM, Broadbent JM, Poulton R, Locker D. Long-term dental visiting patterns and adult oral health. J Dent Res. 2010;89:307–11.
45. Astrøm AN, Ekback G, Ordell S, Nasir E. Long-term routine dental attendance: influence on tooth loss and oral health-related quality of life in Swedish older adults. Community Dent Oral Epidemiol. 2014;42:460–9.
46. Grytten J, Holst D. Do young adults demand more dental services as their income increases? Community Dent Oral Epidemiol. 2002;30:463–9.
47. Chrisopoulos S, Luzzi L, Brennan DS. Trends in dental visiting avoidance due to cost in Australia, 1994 to 2010: an age-period-cohort analysis. BMC Health Serv Res. 2013;13:381.
48. Manski RJ, Vargas CM, Brown E, Carper KV, Macek MD, Cohen LA. Dental procedures among children age birth to 20, United States, 1999 and 2009. J Public Health Dent. 2015;75:10–6.
49. Manski RJ, Macek MD, Brown E, Carper KV, Cohen LA, Vargas CM. Dental service mix among working-age adults in the United States, 1999 and 2009. J Public Health Dent. 2014;74:102–9.
50. Teusner DN, Amarasena N, Satur J, Chrisopoulos S, Brennan DS. Applied scope of practice of oral health therapists, dental hygienists and dental therapists. Aust Dent J. 2016;61:342–9.
51. Teusner DN, Amarasena N, Satur J, Chrisopoulos S, Brennan DS. Dental service provision by oral health therapists, dental hygienists and dental therapists in Australia: implications for workforce modelling. Community Dent Health. 2016;33:15–22.
52. Eklund SA. Changing treatment patterns. J Am Dent Assoc. 1999;130:1707–12.
53. Eklund SA. Trends in dental treatment, 1992 to 2007. J Am Dent Assoc. 2010;141:391–9.
54. Brennan DS, Balasubramanian M, Spencer AJ. Trends in dental service provision in Australia: 1983–1984 to 2009–2010. Int Dent J. 2015;65:39–44.
55. Brennan DS, Ryan P, Spencer AJ, Szuster FS. Dental service rates: age, period, and cohort effects. Community Dent Health. 2000;17:70–8.
56. Ju X, Spencer AJ, Brennan DS. Dentist age, period and cohort effects on provision of dental services in Australia: 1983-84 to 2009-10. Community Dent Oral Epidemiol. 2017;45:242–50.
57. Ju X, Teusner DN, Spencer AJ, Brennan DS. Longitudinal changes in proportions of dental services provided by Australian dentists, 1983 to 2010. JDR Clin Trans Res. 2017;2:109–18.
58. Spencer AJ, Brennan DS, Szuster FSP. Trends in work effort among private general practitioners. Int Dent J. 1994;44:|223–9.
59. Glass KP, Anderson JR. Relative value units: from A to Z (Part I of IV). J Med Pract Manage. 2002;17:225–8.
60. Clappison RA, Pressey WW, Freeman RC. Relative value method of fee determination. J Can Dent Assoc. 1965;31:763–78.
61. Tuominen R, Tuominen M. Relative value of dental procedures. Community Dentistry Oral Epidemiol. 1994;22:319–22.
62. Schwarz E. Dental treatment provided to young adult Danes enroled in alternative dental programs during a 3-year period. Acta Odontol Scand. 1989;47:159–65.
63. Marcus M, Koch AL, Schoen MH, Tuominen R. A proposed new system for valuing dental procedures. Med Care. 1990;28:943–51.
64. Council on Dental Health: Bureau of Economic Research and Statistics, Study of relative values of dental services. J Am Dent Assoc. 1968;76:117–22.
65. Teusner DN, Ju X, Brennan DS. Dental responsibility loadings and the relative value of dental services. Aust Dent J. 2017;62:372–7.
66. Brennan DS, Ju X, Teusner DN. Components of responsibility in estimating relative value units: how do dentists value their work? Community Dent Oral Epidemiol. 2018;46:385–91.
67. Elderton RJ. Preventive (evidence-based) approach to quality general dental care. Med Princ Pract. 2003;12:12–21.
68. Elderton RJ, Davies JA. Restorative dental treatment in the General Dental Service in Scotland. Br Dent J. 1984;157:196–200.
69. White JM, Eakle WS. Rationale and treatment approach in minimally invasive dentistry. J Am Dent Assoc. 2000;131:13S–9S.
70. Brennan DS, Spencer AJ. Service patterns associated with coronal caries in private general dental practice. J Dent. 2007;35:570–7.
71. Yip K, Smales R. Oral diagnosis and treatment planning: part 5. Preventive and treatment planning for dental caries. Br Dent J. 2012;213:211–20.
72. Brennan DS, Balasubramanian M, Spencer AJ. Treatment of caries in relation to lesion severity: implications for minimum intervention dentistry. J Dent. 2015;43:58–65.
73. Wennberg J. Which rate is right? N Engl J Med. 1986;314:310–1.
74. Bailit H, Clive J. The development of dental practice profiles. Med Care. 1981;19:30–46.
75. Bader JD, Shugars DA. Variation, treatment outcomes, and practice guidelines in dental practice. J Dent Educ. 1995;59:61–95.
76. Grembowski D, Milgrom P, Fiset L. Dental decision making and variation in dentist service rates. Soc Sci Med. 1991;32:287–94.
77. Bader JD, Shugars DA. Variation in dentists' clinical decisions. J Public Health Dent. 1995;55:181–8.
78. Grembowski D, Milgrom P, Fiset L. Factors influencing variation in dentist service rates. J Public Health Dent. 1990;50:244–50.
79. Brennan DS, Spencer AJ, Szuster FSP. Rates of dental service provision between capital city and noncapital locations in Australian private general practice. Aust J Rural Health. 1998;6:12–7.

80. Spencer AJ, Lewis JM. Service-mix in general dental practice in Australia. Aust Dent J. 1989;34:69–74.
81. Manning WG, Bailit HL, Benjamin B, Newhouse JP. The demand for dental care: evidence from a randomized trial in health insurance. J Am Dent Assoc. 1985;110:895–902.
82. Brennan DS, Spencer AJ, Szuster FSP. Insurance status and provision of dental services in Australian private general practice. Community Dent Oral Epidemiol. 1997;25:423–8.
83. Brennan DS, Spencer AJ. Influence of patient, visit and oral health factors on dental service provision. J Public Health Dent. 2002;62:148–57.
84. Brennan DS, Spencer AJ. The role of dentist, practice and patient factors in the provision of dental services. Community Dent Oral Epidemiol. 2005;33:181–95.
85. Gilbert GH, Gordan VV, Korelitz JJ, Fellows JL, Meyerowitz C, Oates TW, Rindal DB, Gregory RJ. Provision of specific dental procedures by general dentists in the National Dental Practice-Based Research Network: questionnaire findings. BMC Oral Health. 2015;15:11.
86. Gordan V, Riley JL III, Geraldeli S, Rindal DB, Qvist V, Fellows JL, Kellum HP, Gilbert GH. Repair or replacement of defective restorations by dentists in The Dental Practice-Based Research Network. J Am Dent Assoc. 2012;143(6):593–601.
87. McCracken MS, Gordan VV, Litaker MS, Funkhouser E, Fellows JL, Shamp DG, Qvist V, Meral JS, Gilbert GH. A 24-month evaluation of amalgam and resin-based composite restorations. Findings from The National Dental Practice-Based Research Network. J Am Dent Assoc. 2013;144:583–93.
88. Heaven TJ, Gordan VV, Litaker MS, Fellows JL, Rindal DB, Firestone AR, Gilbert GH. Agreement among dentists' restorative treatment planning thresholds for primary occlusal caries, primary proximal caries, and existing restorations: Findings from The National Dental Practice-Based Research Network. J Dent. 2013;41:718–25.
89. Valderas JM, Alonso J. Patient reported outcome measures: a model-based classification system for research and clinical practice. Qual Life Res. 2008;17:1125–35.
90. Fiske J, Gelbier S, Watson RM. The benefit of dental care to an elderly population assessed using a sociodental measure or oral handicap. Br Dent J. 1990;168:153–6.
91. Petersen PE, Nortov B. The effect of a three-year trial of a community dental care program for aged pensioners in Denmark [in Danish]. Ugeskr Laeger. 1995;157:2712–6.
92. Locker D. Does dental care improve the oral health of older adults? Community Dent Health. 2001;18:7–15.
93. Fisher MA, Gilbert GH, Shelton BJ. Effectiveness of dental services in facilitating recovery from oral disadvantage. Qual Life Res. 2005;14:197–206.
94. Crocombe LA, Brennan DS, Slade GD. The influence of dental attendance on change in oral health–related quality of life. Community Dent Oral Epidemiol. 2012;40:53–61.
95. Brennan DS, Spencer AJ, Roberts-Thomson KF. Change in self-reported oral health in relation to use of dental services over 2 yr. Eur J Oral Sci. 2012;120:422–8.

Further Reading

Aday LA. Establishment of a conceptual base for health services research. J Health Serv Res Policy. 2001;6:183–5.
Donabedian A. The quality of care. How can it be assessed? JAMA. 1988;260:1743–8.
Grembowski D, Andersen RM, Chen M. A public health model of the dental care process. Med Care Res Rev. 1989;46:439–96.

Bioethics of Epidemiological Oral Health Studies

Jonathon Timothy Newton

Contents

27.1 Codes of Conduct for Research – 410
27.1.1 The Nuremberg Code [3] – 410
27.1.2 The Declaration of Helsinki [4–6] – 410
27.1.3 The Belmont Report [7] – 411

27.2 The Implications of Ethical Principles for the Conduct of Bioethical Research – 411
27.2.1 Respect for the Individual – 411
27.2.2 Justice – 413
27.2.3 Beneficence – 415

27.3 Ethical Review Processes/Institutional Review Boards – 416

27.4 Summary – 416

References – 417

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_27

27

Learning Objectives

After reading this chapter you will be able to:

- Recognise the importance of ethical considerations in the conduct of biomedical research
- Describe the history of the development of ethical guidance from the Nuremberg code of 1947 to the modern day
- List and describe the core principles of the ethical conduct of biomedical research
- Reflect on the application of the core ethical principles of: Respect for the individual, justice and beneficence for the conduct of your own research.

Researchers are morally bound to protect the rights and dignity of those individuals who participate in research [1]. Furthermore the ethical conduct of research involves the engagement in activities which enhance the integrity of the research, thus increasing the trustworthiness and value of the research [2]. The development of guidance in this area has been influenced by the broader discipline of moral philosophy. Approaches to ethics can largely be divided into two models: The application of broad moral imperatives and the approach of utilitarianism – balancing the benefits and harms of any decision. In general, codes of research ethics tend to include aspects of both approaches, with broad principles of doing good and respecting the individual being paramount, but with an awareness of the need to balance the risks and benefits of participation. Institutional Review Boards (in some contexts referred to as ethical committees) are the organisations responsible for reviewing proposed research and ensuring that the planned conduct of the research adheres to the ethical principles outlined in the codes of practice.

27.1 Codes of Conduct for Research

27.1.1 The Nuremberg Code [3]

Prior to 1947 here was no single unified code of conduct for research involving human participants, though it had been widely accepted that the practice of research should follow ethical principles. Widespread condemnation of the practices identified during the Nuremberg trials of 23 German doctors including Karl Brandt following World War II led to the first code of practice for research involving human participants. The Nuremberg Code comprises ten directives:

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject.

The code was not well received initially, and there was a widespread perception that it only applied to misconduct, rather than being guiding principles for the development of research protocols. However the code was influential in the development of the Declaration of Helsinki [3].

27.1.2 The Declaration of Helsinki [4–6]

Originally produced by World Medical Association in 1964, the Declaration of Helsinki sought to create a framework that would provide the public with assurances that the rights, safety and well-being of any participant in a research trial are protected and that the data arising from such trials is credible. Since the origi-

nal declaration was published in 1964, there have been seven updates and two clarifications (the most recent being in 2013), but the principles underlying the declaration remain the same. These fundamental principles are:

- Respect for the individual. The implications of this for the conduct of research include respect for the individual's right to self-determination and the right to make informed decisions regarding participation or nonparticipation in research, both initially and during the course of the research. It is clear that consent to participation in research is an ongoing process and that the individual participant can withdraw their consent at any point.
- Within the scope of the general principle of justice, the Declaration of Helsinki states that there is a need for special vigilance with regard to the protection of the rights of vulnerable individuals and groups. It is recognized that when the research participant is incompetent, physically or mentally incapable of giving consent, or is a minor, then allowance should be considered for surrogate consent by an individual acting in the subject's best interest, although their consent should still be obtained if at all possible.
- Beneficence. Whilst the declaration focusses on ensuring that the benefits of conducting the research must outweigh the risks and harms, the declaration makes it explicit that the investigator's duty is solely to the participant. Research is a key activity which generates new knowledge and understanding for the benefit of humankind; however the welfare of participants must always take precedence over the interests of science and society.
- Ethical considerations must always take precedence over laws and regulations. The moral duty of the researcher is given precedent over the laws and regulations of society.

27.1.3 The Belmont Report [7]

Between the years of 1932 and 1972, the US Public Health Service in conjunction with the University of Tuskegee conducted a longitudinal observational study of the natural progression of untreated syphilis. The 600 participants were socially deprived farm workers from the African American community, who were told that the study would last for 6 months but who were followed up for 40 years. The true nature of the study was not fully revealed; participants were informed that the study was looking at the treatment of 'bad blood' and were informed that they would receive 'special treatments' which in fact were data collection procedures such as collection of cerebral spinal fluid by spinal tap. The men were given free medical care, meals and free burial insurance for participating in the study which given their poverty was a significant incentive to participate. The participants were not treated with penicillin when it became an acknowledged and effective treatment for syphilis in 1947. Furthermore they were actively discouraged and prevented from seeking any treatment outside the study, including 200 men who were advised to receive treatment when they joined the armed forces. At the termination of the study, 28 participants had died of syphilis, 40 wives of participants had contracted the disease, and 19 children had been born with congenital syphilis.

In 1997 the then US President, Bill Clinton, issued an official apology to the participants and others harmed as a result of the study.

The US Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 and charged the commission with identifying the ethical principles that should guide all research involving human participants and with developing guidelines for the conduct of ethical research involving human participants. These were enshrined in the Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research which was published in 1979 [7].

The Belmont Report identified three principles essential to the ethical conduct of research with humans:

1. Respect for persons
2. Beneficence
3. Justice

There is a clear parallel between these principles and those enshrined in the Declaration of Helsinki.

27.2 The Implications of Ethical Principles for the Conduct of Bioethical Research

27.2.1 Respect for the Individual

The principle of respecting the rights of an individual to self-determination has been expressed in many ways, but common to all definitions is the view that all individuals should be treated as autonomous agents, who are able to consider the potential harms and benefits of a situation, analyse how those risks and potential benefits relate to his or her personal goals and values and take action based on that analysis. The practical implication of the application of this principle is the process of informed consent. Prospective research participants must be given the information they need to determine whether or not they wish to participate in a particular research project which has been explained to them to their satisfaction. There should be no pressure to participate and ample time to decide. Respect for persons demands that

participants enter into the research voluntarily and with adequate information and that the giving of consent to participation should be considered as an ongoing decision which can be withdrawn during or after participation. The International Conference on Harmonisation for Good Clinical Practice in clinical trials states:

> Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
>
> ICH-GCP Glossary 1.28 [8]

The three fundamental aspects of informed consent are:

27.2.1.1 Voluntariness

Individuals' decisions about participation in research should not be influenced by anyone involved in conducting the research or by any member of their friends, family or carers. This would include the application of undue incentives to participation, which is discussed below with regard to the benefits and risks of participation.

27.2.1.2 Comprehension

Investigators are responsible for providing information during the informed consent process in a manner that is understandable to the potential participants. This may mean adjusting the reading levels of documents provided or translating documents and presentations into the language with which participants are most comfortable or the use of alternative communications systems such as photographs or symbols.

27.2.1.3 Disclosure

The researcher, in providing information to potential participants, should disclose a range of information to the potential participants. Whilst the requirements differ across settings and countries, most include the following as a minimum:

1. The purpose of the study and what participation would involve. Emphasis should be placed on the voluntary nature of participation, duration and burden of participation.
2. Any reasonably foreseeable risks to the individual. Ideally risks should be stated in realistic terms using language and analogies that are understandable to any potential participants.
3. Potential benefits to the individual or others.
4. The alternatives to the research protocol.
5. The extent of confidentiality protections for the individual. This would also include whether any information may be used at a later point for research other than that stated in the information sheet. Where research may involve potential disclosure by the participant of criminal activity or unsafe professional practice (e.g. in the case of studies where the participants are health or social care practitioners), the limits of confidentiality should be identified.
6. Compensation in case of injury due to the protocol.
7. Contact information for questions regarding the study, participants' rights and in case of injury.
8. The conditions of participation, including right to refuse or withdraw without penalty.
9. Whether research material could be de-identified and used for other research without additional consent.

Given that consent is an ongoing process, disclosure should not be seen as a one-off event taking place only at the initial stage of recruitment but an ongoing process whereby participants are made of any new relevant information arising during the research.

In some cultures and settings, it may not appropriate to obtain informed consent solely from the individual participants, because the individual's interests may be considered to be intimately entwined with their community's interests. The appropriate way to attain community consent may vary widely but is often achieved through meetings with large groups of community representatives or community leaders. For example, in New Zealand specific guidance is issued on the process and guidance for consulting with the Maori community on proposed research [9].

A particular example of a problematic situation for informed consent is emergency medicine, particularly in situations where the patient may be unconscious or in danger of losing their life. In general, consent in such situations would be taken on the basis of whether the patient might reasonably consent if they were able. Furthermore, the participant's consent should be sought as soon as is possible. There should also be in place guidance for the safe destruction of any data collected should the participant withdraw the consent.

Records documenting that informed consent has been obtained should be maintained. Typically researchers would ask that participants complete a written consent which is then counter signed by the researcher, with copies being held by both parties. IRBs and ethics committees are conscious that alternative approaches may be necessary or appropriate such as where literacy levels are low or where the maintenance of written records could place the participant at risk. One common exception is where participation involves only the completion of a questionnaire, where the perception is that the additional burden of completing a consent form is superfluous given the implied consent of completing the questionnaire. Such exceptions would require an ethical justification, as opposed to pragmatic grounds such as ease or convenience.

Case Study: Opt-in Versus Opt-out Consent in Epidemiological Surveys

Many historical large-scale epidemiological surveys, particularly those involving children sampled from schools, relied on opt-out consent, that is, the children and their parents were given detailed information on the research and then asked to respond only if they wished that their child did not participate in the research. Recent changes in legislation in many countries regarding the protection of individual data have meant that opt-in procedures are now required for such surveys, that is, that a positive, active intention to participate must be expressed. White et al. [11] have argued that this endangers the validity of such research through decreasing the effective response rate and having a particular impact on the participation of certain groups. They cite the example of a school-based survey conducted in 1982 with opt-out consent where all children of the appropriate age attending the school participated. A parallel survey in 2002 using an opt-in consent procedure recruited only 49% of the eligible children.

This is perhaps a case where two important ethical principles act against each other. The principle of Respect for Autonomy emphasises the importance of the individual choice in participation, but this may have an impact on the representation of particular groups, which falls within the principle of justice.

White et al. [10].

27.2.2 Justice

The definition of justice has two parts:

- That fair procedures are used to select potential research participants.
- There is a fair distribution of benefits and burdens to populations who participate in research.

This definition draws on notions of both social justice and individual justice. Individual justice requires that investigators 'should not offer potentially beneficial research only to some patients who are in their favour or select only 'undesirable' persons for risky research' [7]. Social justice, 'requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons' [7].

Equity vs. Equality in Human Subjects Research

The differentiation of equity and equality will be familiar to those involved in the exploration of the social determinants of health and oral health inequalities. Researchers should strive for equitable distribution of the risks and potential benefits of the research. This means that investigators are treating the groups involved in the research fairly and justly. It does not necessarily mean that all groups are equally represented but that their representation is fair and just based on the risks and potential benefits associated with the research.

To achieve an equitable distribution of the risks and potential benefits of research, investigators must determine the distribution of different groups (men and women, racial or ethnic groups, adults and children, age, etc.) in the populations that:

1. May be affected by the disease or condition under study
2. That are anticipated to benefit from the knowledge gained through the research

Investigators must ensure that the participants recruited for research will not be unduly burdened and that recruitment reflects the diversity of the population that may benefit from the knowledge generated from the study. One often unintended consequence of research is that benefits accrue to those whose financial, educational and social position confers advantage, since they may be better able to afford new and costly treatment or may have better access to health care that offers clinical trials for new treatments than individuals in resource-poor settings.

27.2.2.1 Justice in the Selection of Potential Participants

Justice requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research. The principle of justice may arise in decisions about inclusion and exclusion criteria for participation in research and requires investigators to question whether groups are considered for inclusion simply because of their availability, their compromised position or their vulnerability – rather than for reasons directly related to the problem being studied. The challenge of applying the principle of justice is how to decide which criteria should be used to ensure that harms and benefits of research are equitably distributed to individuals and populations.

IRBs/ethical review committees as well as funding bodies such as the National Institute of Health set expectations of the recruitment of minority ethnic communities and other under-represented groups within research, requiring that researchers identify a strategy for ensuring equitable representation of such groups in sampling frames. Similarly representation of individuals across the lifespan should be considered [11, 12].

An individual's potential to participate in research may also be affected by their perceived capacity for autonomous decision-making. The assumption that an individual has autonomy to decide on their participation may be subject to several factors including age, cognitive impairment, illness and medical treatments. An assessment of the individual's capacity to consent to a particular study should be made based on whether their level of capacity is adequate to be able to understand the particular study in question sufficiently well to consent to participate. Thus the notion of capacity to consent to participate is proportional to the complexity of the study. There should be no a priori assumption of lack of capacity. Some individuals may be only temporarily or intermittently incapacitated (e.g. due to injury or medications), and research staff should attempt to approach these individuals at a time when they anticipate the person will have the capacity to consent to research. If a participant regains the capacity to consent to research after the research has begun, investigators should obtain the participant's informed consent before continuing his or her participation in the study. Furthermore if there is a potential that participants may lose capacity to consent during the course of the research, then the researchers will be asked by the IRB/ethics committee to consider what they would do in those circumstances and to inform potential participants of what the procedure would be and what would happen to any data collected up to the point where capacity is lost.

Because research involving a pregnant woman may affect the woman, the foetus or both the woman and the foetus, additional issues must be considered for studies of pregnant women, specifically the impact on both the woman and her foetus.

Prisoners are presumed to be vulnerable to undue pressure to participate in research, in particular that participation may lead to benefits such as increased activity, attention, enhanced good behaviour record, etc. which would not be available to non-participants. Researchers should be explicit in stating that such benefits do not accrue with participation.

The age at which a person is deemed to be an adult for research purposes varies from country to country (e.g. in the United States, it is 18 years, whereas in the United Kingdom, it is 16). However defined children are generally perceived to not have full capacity to provide informed consent for participation. However it is generally agreed that the assent of the child should be sought where possible, that is, that the child should express willingness to participate, in addition to the parents/guardians giving their consent for the child's participation. Both assent and consent should be in place and properly documented.

The age, maturity and psychological state of the child involved in the research should be taken into account when determining whether children have the capacity to assent.

The content and language of the assent process should be appropriate to the age and education/developmental stage of the children providing assent. It may be necessary to have multiple assent documents or assent processes if the children to be enrolled in the research are of different ages or at different stages of development.

27.2.2.2 Justice in Distribution of the Benefits and Risks of Research Amongst Participants

The nature of the possible benefits and risks of participation in research will be discussed below, but for the purposes of this exploration of the justice of distributing the benefits and risks of research, three areas will be explored: The use of placebo controls in trials, the use of deception in obtaining consent and research taking place in developing countries conducted by researchers from more affluent settings.

When placebos are used as a control comparison to a treatment which is presumed to be more active, prospective research participants must be treated fairly which includes being informed what a placebo is, providing the understanding that they are at risk of receiving a placebo treatment and the magnitude of that risk. Only in this way can the potential participant give their informed consent. Placebos should only be used as a control, when there is no approved, effective treatment which would constitute the standard of care for the condition under investigation. Researchers cannot withhold an effective treatment for the purposes of research.

The principles of informed consent require that participants are given full and detailed information about the nature and purpose of the research. Incomplete disclosure of the goals of the research and deception is sometimes permissible (and is often used in psychological research), but researchers may only adopt deception if:

- The scientific goals of the research cannot be achieved by methods that do not involve incomplete disclosure or deception.
- There is evidence to suggest that participants would be willing to participate in the research if they were fully cognisant of the purpose of the study.
- Participants are given a full debriefing outlining the full information and allowing them to withdraw their data given the new information, at a point as soon as possible after their participation.

The situation where researchers from developed countries conduct research in developing countries, especially when the research involves access to resources, such as medicines or other interventions, which would not normally be available in that country, creates a number of ethical dilemmas. There may be a perception that such research could be exploitative particularly since potential participants may have few options outside volunteering for the research. Furthermore how can sustainable change be created after the research is complete, both for the current and future populations.

27.2.3 Beneficence

The principle of beneficence, whilst generally being taken to refer to the injunction to 'Do no harm', also implies a broader duty to maximise possible benefits and minimise possible harms. As most healthcare professionals will recognise there are few interventions that purely give benefit, most involve some degree of harm or risk of harm which must be balanced against the benefits. IRBS will ask that investigators maximise the benefits and minimise the risk of participating in a research investigation.

Assessing risks and potential benefits is inexact, but investigators need to be able to explain to the IRB and the potential research participants how and why the potential benefits of research outweigh the risks of participating in a particular study.

Most IRBs and ethics committee will have a system of ethical review which is risk based, that is, the extent of the review will be proportionate to the level of risk implied by the research methods. Minimal or low risk studies will be those where the risks of participation are considered to be no greater or only marginally greater than the risks normally encountered in everyday life by the potential participants. Note that once again, the researcher must consider the context of the research – the level of risk of the research is compared to the individual's non-research activities.

Perhaps the most obvious risks of biomedical research would be the physical risks, including pain, injury and sensory impairment. These risks may be brief or extended, temporary or permanent, occur during participation in the research or arise after. They may also have an impact on close relatives of the participant. In many situations, physical risks in research can be minimised by carefully and skillfully following protocols, by having trained individuals conduct research procedures, through careful monitoring of research participants' health status, by recruiting appropriate populations and by providing clinical care when needed.

Psychological risks may include anxiety, sadness, regret and emotional distress, amongst others, particularly where researchers might seek to temporarily induce these states as part of the research. However, psychological risks may also exist in all studies, for example, if participants are asked to talk about difficult personal topics. Possible ways to protect against psychological risks include reminding participants of their right to withdraw from research or limit their participation if they become uncomfortable, providing counselling or psychological support for participants who experience distress, or thoroughly debriefing research participants after research sessions are completed.

Where it is possible that an individual's participation in research or the disclosure of the data they contributed to the research could result in a negative impact on how people view the participant, then the risk is of a Social nature. Social risks can range from jeopardizing the individual's reputation and social standing, to placing the individual at risk of political or social reprisals. Examples might include research into homosexuality in countries where homosexuality is illegal or recruiting participants from minority ethnic communities that are subject to prejudice in their society. Often, minimizing social risks to participants involves protecting confidential data, including not only the data collected but the fact of participation in the research project itself. One example of this as discussed earlier may be the instance where consent forms are not completed since the written record could place the participant at risk. The need for maintaining confidentiality of private information exists in virtually all studies in which data are collected from or about living individuals. In most research, maintaining confidentiality is a matter of following some established practices, for example:

- Properly disposing of data sheets and other paper records
- Limiting access to identified data
- Storing research records in locked cabinets or secured databases

It may also be appropriate for investigators to remove direct identifiers from human specimens and data so that they may be analysed without risk of accidental disclosure of private information. De-identifying data can be done in several ways, including the use of secure codes and anonymisation of data sets. As a general principle unless there is a good reason why your data need to be identifiable, all data should be anonymised.

Legal risks include the exposure of activities of a research subject that could reasonably place the subjects at risk of criminal or civil liability.

Economic risks may exist if knowledge of one's participation in research, for example, could make it difficult for a research participant to retain a job or to find a job or if insurance premiums increase or loss of insurance is a result of the disclosure of research data. Protecting

confidentiality of data is one method for protecting against economic risks, such as those to employability and insurability. Investigators may elect to keep research data separate from medical records in order to prevent employers and insurance companies from obtaining information that could put the participants at risk.

If participation in research involves a significant commitment from participants in terms of time or effort, investigators may wish to provide compensation to reimburse them for these inconveniences. However in providing compensation, it is important that the compensation does not unduly incentivise the individual to participate. During the informed consent process, investigators should explain to potential research participants whether the participant will receive compensation for their participation in the research and how and when the compensation will be received, especially if research participants withdraw prior to the study's completion, and will they still receive the anticipated compensation. Compensation should not be presented as a benefit of the research; otherwise it may exert an undue influence, meaning that potential participants feel unable to evaluate potential research risks and make appropriate judgements about participation. It may also prompt subjects to conceal information that would exclude them from enrolling or continuing in a research study. Investigators should carefully consider compensation and other inducements with respect to potential participants' characteristics such as their financial and employment status, emotional state and community and other resources. The timing of compensation payments may be critical since some individuals may not be able to maintain credit if they are required to wait for a long time before reimbursement of travel expenses.

Biomedical research often involves examinations and investigations which can be used routinely in diagnostic settings. These aspects of a research protocol may benefit participants by helping them to better understand a disease or condition and may influence the participants' medical decision-making. The risk is that research participants may misunderstand the benefits of research if they think that potential benefits of participation in research are certain. This is called the therapeutic misconception. It relates in part to the researcher's duty to act in equipoise; the researcher should not indicate that they believe any intervention to be superior in the study. A state of 'equipoise' is required for conducting research that may pose risks to research participants, particularly for clinical trials. For a clinical trial to be in equipoise, there must be true uncertainty amongst professionals about whether one treatment is better than another. Equipoise is essential for obtaining generalizable knowledge.

As with informed consent, special provisions may need to be made for vulnerable groups, or those with dependent relationships with the researcher, for example, teachers conducting studies involving their own students, or students participating in research for course credit. The researcher must consider carefully how they avoiding influencing the potential participants' decisions either through threats of harm (coercion) or through excessive compensation (undue influence).

27.3 Ethical Review Processes/Institutional Review Boards

As a consequence of the requirements for closer governance of research, systems of ethical review have been developed. The committees responsible for ethical review are variously known as Institutional Review Boards (IRBs, notably in the United States) or ethics committees (typically in the United Kingdom). These are specialized committees required by national regulations that safeguard the rights and welfare of human subjects. The roles of IRBs/ethics committees vary across countries but generally include:

- Initial review and approval of the proposed research activity according to ethical principles
- Review of the proposed informed consent process
- Providing continuing monitoring of the research through progress reports and recording of the final outcomes of the research

IRBs are expected to draw their membership from a variety of backgrounds, including expertise in research methodologies, statistics and the lay perception of research.

27.4 Summary

Bioethical research requires an understanding of the ethical principles that guide good research practice: Respect for the autonomy of individuals, beneficence, justice and the primacy of the ethical imperative. In applying these principles, researcher must give considerable thought to how to communicate effectively with the potential and actual participants before, during and after the trial. The Institutional Review Boards/ethical review committees exist to review the conduct of research in order to ensure the rights if participants are protected and that society in general can rely on the findings of biomedical research as being independent and trustworthy.

References

1. British Medical Association. Medical ethics today: the BMA's handbook of ethics and law. 3rd ed. Chichester: Wiley-Blackwell; 2012.
2. United Kingdom Research Integrity Office. Code of Practice for Research: promoting good practice and preventing misconduct. http://www.ukrio.org/ukR10htre/UKRIO-Code-of-Practice-for-Research1.pdf. Accessed 02.10.2019.
3. Weindling P. The origins of informed consent: the international scientific commission on medical war crimes, and the Nuremberg code. Bull Hist Med. 2001;75(1):37–71.
4. World Medical Association. WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed 02.10.2019.
5. Frewer A, Schmidt U, editors. History and theory of human experimentation: the declaration of Helsinki and modern medical ethics. Stuttgart: Franz Steiner Verlag; 2007.
6. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. Br Med J. 2007;335(7621):624–5.
7. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Department of Health, Education and Welfare (DHEW). The Belmont Report (PDF). Washington, D.C.: United States Government Printing Office; 1975.
8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). https://www.ich.org/page/ich-guidelines. Accessed 02.10.2019.
9. New Zealand Health Research Commission. Guidelines for Maori research ethics. http://www.hrc.govt.nz/sites/default/files/Te%20Ara%20Tika%20Guidelines%20for%20Maori%20Research%20Ethics.pdf. Accessed 06.09.2019.
10. White DA, Morris AJ, Hill KB, Bradnock G. Consent and school based surveys. Br Dent J. 2007;202:715–7.
11. National Institute for Health. NIH Policy and Guidelines on the inclusion of women and minorities as subjects in clinical research. http://grants2.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Accessed 02.10.2019.
12. Food and Drug Administration Agency. Guidance on the inclusion of minority groups in research. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126396.pdf. Accessed 02.10.2019.

Further Reading

The National Institute for Health (NIH) provides an excellent on line training course in bioethics for researchers, particularly those who hold a grant award from the NIH. This can be accessed at: http://phrp.nihtraining.com/users/login.php.

NIH Centre for Bioethics provides a large number of guidance documents and an archive of published articles in the bioethics field https://www.bioethics.nih.gov/home/index.shtml.

NIH: Research Ethics: How to treat people who participate in research https://www.bioethics.nih.gov/education/pdf/FNIH_BioethicsBrochure_WEB.PDF. A very useful introductory guide to ethical principles and their application in biomedical research.

Gray FD. The Tuskegee syphilis study: an Insider's account of the shocking medical experiment conducted by government doctors against African American men. Montgomery: NewSouth Books; 2002.

Jones JH. Bad blood: the Tuskegee Syphilis experiment. New York: The Free Press; 1992. Two excellent accounts of the infamous study.

Epidemiology, Politics, and Dental Public Health

Carol C. Guarnizo-Herreño, Paulo Frazão, and Paulo Capel Narvai

Contents

28.1 Introduction – 420

28.2 New Public Health – 422

28.3 Dental Public Health – 423

28.4 Theoretical Basis of the Influence of Social Policies on Population Oral Health and Inequalities – 425

28.4.1 How Social Policies Affect Oral Health and Inequalities? – 425

28.5 Evidence on the Relationship Between Social Policies and Population Oral Health (Including Inequalities) – 426

28.5.1 General Political Factors and Oral Health – 426

28.5.2 Certain Specific Social Policies and Population Health – 427

28.5.3 Particular Policies Aimed to Impact Oral Health – 429

28.6 Conclusion – 431

References – 432

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_28

Learning Objectives

- To discuss concepts of knowledge, power, politics, and social policies, and why these are important issues for epidemiology and dental public health
- To identify the main characteristics of the Collective Health (Collective Oral Health) approach which challenges the traditional field of Public Health (Dental Public Health)
- To provide a general overview of the theoretical basis of the influence of social policies on population oral health and inequalities
- To present current evidence on the relationship between oral health (including inequalities) and general political factors, specific social policies and policies aimed to impact oral health

28.1 Introduction

"Knowledge is power," that is the popular saying. There are many reasons for that human conviction that ignores frontiers. Over the centuries, common sense has been strengthening the idea that being well informed is a sine qua non condition to add and keep power. However, "being well informed" is not the same as simply "knowing things" at the practical level. On the contrary, it requires going further than common sense, and for that purpose, one must make use of all kinds of knowledge, so as not to be misled by what appears to be obvious. If one intends to know, one should not ignore its intuition, but must go beyond it. Human experience shows that in many situations – the extreme example would be the war, but also in daily situations–, the difference between knowing and not knowing may correspond to living or dying. The notion "knowledge is power" is also attributed to Francis Bacon, the British philosopher and politician, who held many governmental positions and was widely acknowledged as the founder of empiricism.

Conceiving knowledge as a dimension of power is of extreme political relevance. Everything that relates to power does indeed concern to policies and politics, considering both its strict institutional dimension – public or State policies – and its broad institutional dimension, at the society level – related to political orientations that can be found in all different forms of social organization (family, neighborhood associations, unions, parties, universities, companies, churches, etc.). Led by participation, representation, and direction propositions, class interests, sub-classes, and different social groups are activated, moving the dispute that involves different political orientations and projects, from both the State and the society, in every country or region, creating and transforming what is in place into a continuous and dialectic movement.

Either by producing consensus or as the result of conflicts, politics is a transformer activity, not only of the "objective world," but mainly of the social conscience and its relations with the reality, able to manifest in almost all dimensions of the societal life.

In early decades of the twenty-first century, the world lives the so-called *Information Society*, on account of the levels in obtaining, circulating, and analyzing data – and, no doubt, considering what it means for the economy, decisively influencing the production of goods and services worldwide [1]. Every day, communication media divulge data in amount humanity has never seen before. However, one may notice in this volume of information a lot of communication rubbish, frivolities, and worthless data.

In this second decade of the twenty-first century, around 1 billion people worldwide use some form of digital media (Facebook, Twitter, YouTube, etc.) for seeking information related to different topics, including health. The conflicting information in the media is increasing, and Public Health can be encountering an emerging threat of "digital pandemics," the rapid, far-reaching spread of free and scientifically inaccurate health information across the Web [2]. As a result, also the information selection is crucial when it comes to power, with ever-growing relevance. Thus, concerning politics, the saying "knowledge is power" requires considering the quality of information, the nature of the knowledge at issue.

Epidemiology – a knowledge area in the public health field defined by Last as "the study of the distribution and determinants of health-related states or events in specific populations, and the application of this study to the control of health problems" [3] – produces scientific knowledge by engendering a kind of information that carries strategic value. As such, it raises interest among social groups that keep some power and assigns both meaning and political relevance to that knowledge. According to Carvalho [4], epidemiologists study "the determinants and conditions for illness and health problems to occur amidst human populations." By getting involved with "determinants" and "occurrence conditions" of diseases and health problems, epidemiology brings to its scope not only biological events, but everything that will somehow take part, either directly or indirectly, as determinant, a conditioning factor, or the main reason for the distribution of diseases and health conditions. In other words, it deals with both biological and non-biological causes.

Terris [5] identifies the following functions for epidemiology:

1. Elucidating the agent, the host, and environmental factors that affect health, aiming at establishing the scientific grounds for prevention of diseases and health conditions

2. Determining the relative relevance of causes for the disease, aiming at establishing priorities for both research and action
3. Identifying population segments that face more severe risks of getting ill due to specific causes, aiming at pointing out proper actions
4. Evaluating the efficacy of health services and programs concerning health promotion amidst the population

Identifying what to do and pointing out measures to be taken are tasks to be assigned to the public health professional, and decision-making depends on multiple aspects related to both the structure and the conjuncture of the concrete social reality, which are determined at the political sphere. As feudalism decayed and the modern State was built, intense economic and social changes occurred, giving rise to many diseases. Health issues are an interesting subject for those in power as a collective phenomenon and became part of the political agenda [6].

The idea of the population is a central point in epidemiology – as in politics. To Almeida-Filho [7], "from a more critical perspective, one may propose that, instead of illness (an essentially clinical notion), the object in epidemiology is the relation between the subgroup of sick individuals and the entire population they belong to, including, consequently, the determinant factors of such relation." On this aspect, Carvalho states, "[…] it is obvious that sickness happens in people, and studying cases is extremely important for epidemiology. However, the epidemiological speech is built up not to talk about the specificity of the individual case, as in the clinical speech, but to talk about the illness as a constituent element in a given social structure" [4]. So, the epidemiological object involves both physical–pathological and clinical objects – respectively, the biological and the individual dimensions of the human body.

Moreover, for its very nature, the epidemiological object is socially determined. Therefore, it is connected to different theoretical models of interpretation of societies – the Social Sciences field – and to different processes for building up its scientific knowledge, the interface between epidemiology and epistemology. For some authors, since the 1970s, but specifically from the last decade of the twentieth century, epistemologists from some Latin-American countries have been discussing critical issues, including debates and theoretical discussions involving the articulation between *macro* and *micro* levels, biological and social aspects, containing methodological contributions that go beyond more traditional approaches marked by logical empiricism [8]. The theoretical debate is extensive and, for obvious reasons, will not be discussed in this chapter.

As a sub-area of public health, epidemiology is not just a "medical branch": it is a field of knowledge and practices that overtop the health area itself: in order to understand the levels of health, diseases, and health conditions, it encloses knowledge produced in areas such as economics, sociology, anthropology, history, etc. Carvalho remarks, "[…] diseases are not events that take place by chance; they are related to a web of other events that can be identified and studied" [4]. Thus, to explain, on scientific grounds, phenomena related to the health–illness process, one must master knowledge that go far beyond the biological dimension of those phenomena. When searching the primary causes of illness, in the sense pointed out by Rose [9], epidemiology must consider aspects resulting from the political situation, how power is practiced, the use of force, the freedom of expression, the consensual spaces, in specific ambiances – and make use of methods and techniques compatible with the analysis in course.

Epidemiology may look over events related to politics and power relations. As a producer of knowledge, culture, and awareness, epidemiology in itself is a means of power; it is subjected to interests and goals aimed at by social forces in conflict. The political sense of epidemiology in a specific context is defined by *who*, in each concrete historical situation, produces or takes over knowledge produced by the epidemiology, and by *which interests* will be fulfilled (and, therefore, which interests it will oppose). The epidemiological practice encompasses three questions: *Where?, When?,* and *Who*? Epidemiological thinking can progress by placing two more questions: *Why?* and *What to do then?* It is worth mentioning the decisive role that several players perform in different scenarios: State institutions, non-governmental organizations, private groups, and social movements.

The critical reflection is appropriate and defies the attitude of part of those who produce epidemiological knowledge (i.e., those who produce means to strengthen power,…), who deny the political dimensions of their intellectual doing. They advocate and stand for a supposed "exemption," a "neutral science" only possible in oneiric reveries. The epidemiologist, like all researchers, does not live and work "in the clouds," he/she is surrounded by the reality where his/her job is carried out and is immersed in it. Therefore, epidemiological knowledge may carry implications either favorable or unfavorable as to a specific status quo, resulting from disputes among different political trends, but will never be neutral. The knowledge is not neutral. It is not "innocent" nor are they, those who produce it (either individually or collectively). In this sense, both the product and the producer present a political dimension, as they both are inexorably immersed into power situations – that is, political situations: always under power and always holding parcels of some power. For that reason, any assumption of neutrality, of indifference, of non-political

practice would be useless, once such determination is external to both the product and the producer.

Therefore, the practice of indifference leads to nothing but an omission, which corresponds to a passive form of participation, not exempting at all the political responsibility, as it will either strengthen or enfeeble some political trend, which means it will always serve some interests and oppose others. It is essential here to clearly distinguish "power" from "government" and from "State": in the social life, power is not concentrated in the State or in "the government," but is rather distributed, in levels of power, unevenly among individuals and collective subjects. Carvalho considers that those who produce epidemiological knowledge "[…] make use of different methods and techniques, according to their comprehension of the world, their theoretical points of view and the purposes of their studies, either immediate or not." [4].

The relations between epidemiology, socio-economic situation, and politics have been referred to by many researchers around the world. Starting at the nineteenth century, with epidemics of cholera, typhoid fever, and yellow fever that turned out to be dramatic public health problems and required populational measures, the outstanding contributions by Villermé, Farr, Engles, Chadwick, and Virchow can be mentioned. During the second half of the twentieth century, other authors can be pointed out: Thomas McKeown, Vicente Navarro, and Jaime Breilh. Giovanni Berlinguer analyzes those relations in different historical contexts [10, 11].

The importance of the epidemiological knowledge in the public health practice/theory is undeniable when its arguments are taken over by individual and collective subjects, with specific purposes and becoming a means for reaching "political force." The work by John Snow, producing the kind of knowledge that enabled the control of water distribution of public supply in London, in the middle nineteenth century, to strive against cholera epidemics may be considered a classic expression of that dimension [12].

Many examples could be offered to illustrate the relationship between public health, epidemiology, and politics, highlighting the role researchers, professionals, and other players perform in different forms of social organization as both individual and collective subjects who hold parcels of power that can be put into motion, reaching different levels to the benefit of human emancipation and social justice. Nevertheless, this association is not always marked by an emancipatory sense, nor is always committed to freedom, equality, and democracy. A most significant motion picture in this sense, "Architecture of Destruction" (1989), by Peter Cohen, presents excerpts of films produced by Adolf Hitler government, ascribing upon the Jews the responsibility for propagating tuberculosis and other diseases in Germany. The film also brings out the association of ideas built up by the Nazi, comparing Jews to bacteria, virus, and cancer, intending to justify their genocide project, known as "The Final Solution."

28.2 New Public Health

The public health as a field of knowledge and practices first came up in the Western world in the historical context of the Industrial Revolution, under political predominance of the bourgeoisie. It was meant to enable the maintenance and reproduction of the labor force, through preventing and controlling epidemics. In order to carry out its function, the State granted that social class all necessary means and resources. Therefore, intimately connected to the State, the Public Health attained significant sanitation victories, but, along with those conquests, it transmitted for some people the mental picture of a means for submitting individuals to socially imposed sanitation interests. In other words, it was inexorably associated with social control practices [13].

During the second half of the twentieth century, negative evaluations became more frequent concerning the efficacy of medical practices [14] and public health [15]. In many countries, a "New Public Health" began to characterize different movements and theoretical approaches that proposed breaking up with what was now considered authoritarian practices of the traditional Public Health.

An example, the Lalonde report (1974) launched the basis for a new perspective to deal with health problems at the population level [16]. The new concept stood out health determinants beyond the healthcare system and human biology and included the environment and lifestyle. Some years later, Ashton and Seymour published "The New Public Health" [17], a seminal contribution for the understanding of health service limitations and the need for creating community-based health promotion activities. MacDougall [18] demonstrates the gradual penetration of these new concepts in British and American public health discourses and practices. National and international programs to curb smoking, control drinking and driving, and eradicate drug use have been boosted in challenging the hierarchical dominance of the biomedical model. Health activists in the community, professional associations, political parties, and dedicated civil servants have used this concept to broaden their focus to include the social, economic, and political determinants of health.

One may argue if it actually would represent a new approach, or, on the contrary, just be coming back to those ancient grounds the Public Health was built on [19]. What cannot be denied is that the answers to health challenges "[…] involve stress between approaches based

on medical procedures, which consider the individual medical care as the main responsible for attending health needs and approaches that take medical care as a component that is necessary, but insufficient to face them." [20].

The raising of mortality by non-communicable chronic diseases reinforced the awareness on restraints of the health services structure and the need to think over [17] the idea that the cause of infirmities that affect individuals is not the same of diseases that affect populations [21]. There is, thus, a distinction between two approaches: a wider one, where social determinants associated with lower health levels are identified, and where public health strategies are formulated aiming at the population as a whole; and another one, more specific, aimed at the identification of susceptible individuals that are at risk, and the adoption of measures to protect them. If economic and social determinants are the primary factors of the disease, economic and social policies should be the measures to challenge them [9].

In Brazil, with massive influence on the Latin-American context, some authors came to talk about "Collective Health", referring to the rupture that was to be carried out, proposing it as a new field of knowledge and practices, whose mission would be to take over the traditional Public Health position as it is known nowadays – and therefore, denying it. This new field would have characteristics in opposition to the traditional Public Health in a number of dimensions that include, among others, the comprehension of the health–disease process beyond the biological and medical dimension, but, chiefly, for the protagonist role that is assigned to the society as a whole, and not just to State institutions [22].

According to Paim & Almeida-Filho [22], the "Collective Health" is a "[…] scientific field that produces knowledge on the object '*health*', and in which distinct disciplines operate (the basis of which are epidemiology, health planning/administration and social sciences on health) from different points of view. It is also a field for practices (trans-disciplinary, multi-professional, inter-institutional and trans-sectorial); a field where actions take place in different organizations and institutions, and are carried out by many agents (either specialists or not), inside and outside the space usually acknowledged as the health sector."

One must consider as well that, according to Paim [23], "[…] health actions with collective scope reflect some stress between State and Society, individual freedom and collective responsibilities, private and public interests. How wide and deep those actions may reach depend on the dynamics of each society, especially considering articulations they concretely establish at economic, political and ideological levels." Therefore, collective health models or action guidelines will favor four intervention objects: political (forms of power distribution); practical (changing behaviors; culture; institutions; knowledge production; institutional, professional and relational practices); technical (organization and regulation of resources and productive processes; bodies/environment); and instruments (means for putting intervention in place).

For some researchers, Collective Health is part of the school of thought known as Latin-American social medicine. For others, Latin-American social medicine is considered one among the historical manifestations of the universal phenomenon of the search for social justice, which supposedly has characterized public health worldwide since its inception in Europe and the Americas. From this latter perspective, it is an academic discipline not only in Latin America but in the Anglo-American world as well [24].

Whatever be the perspective, when it comes to historical records, the outcome is yet to be known: will the Collective Health hold on as a new field, epistemic and technological, actually replacing the Public Health, or, on the contrary, will it remain as a theoretical–political movement in the inner part of the Public Health?

The New Public Health actually would represent a new approach, or, on the contrary, just be coming back to those ancient grounds the Public Health was built on? The Collective Health would hold on as a new epistemic field? The answers to these questions will depend on multiple determinants including the historical process in a given time and place in which human beings are inserted in constant interaction with each other and with nature.

28.3 Dental Public Health

Community interventions to address oral health problems have shifted from empiricism to scientific knowledge in the early decades of the twentieth century. This shift occurred when discourse and practice began to leave the philanthropic or charitable orientation based on low-income dental clinics and professional groups linked to public health governmental organizations in the USA, New Zealand, and other parts of the world. The first publications appeared during the 1950s, showing results obtained by applying epidemiological methods in dental caries studies and methods of scientific management in the organization of school dental services.

Previously considered an optional product delivered exclusively within commercial interests, the dental practice changed its social position in developed countries and became an indispensable activity and an essential service for public health. The advances of knowledge on the use of fluorides led to the decline of dental caries burden in many countries of almost all continents.

However, improvements have not yet benefited the poor and disadvantaged populations worldwide. Significant challenges are to translate knowledge and experiences in oral disease prevention and health promotion into action programs and public health policies [25].

During the second half of the twentieth century, Dental Public Health began to expand its thematic field giving rise to new configurations. Although the understanding of this development requires a scientific research effort not yet undertaken, we can hypothesize that Dental Public Health theory has widened; inter and trans-disciplinarities have become increasingly recognized; with ruptures and continuities, transitions and permanence intersecting between the field of traditional Public Health and the New Public Health. It would be important to investigate to what extent current knowledge has been a tributary of this new episteme, whose relations are maintained with traditional concepts and with theoretical perspectives that represent ruptures. In Exley's words [26], it would mean to assess if we are "bridging a gap: the (lack of a) sociology of oral health and healthcare."

In Brazil, the legacy of Dental Public Health has been criticized. The concept of "*Collective Oral Health*" was first presented in the late twentieth century, in the historical context of doubts about the efficacy of the traditional Public Health and the effort for replacing the "Collective Health" as its dialectic oppose. The *Collective Oral Health* was then introduced as an area of knowledge and practices inherent to the Collective Health. If the so-called Public Health Dentistry is an area of the Dentistry, and, simultaneously, of the Public Health, the dialectic denial of Public Health intended by the Collective Health requires bringing up a correspondent in this new epistemological–technological field that may answer questions related to the oral health at the population level – that is, the "Collective Oral Health." As part of this wider whole identified as "Collective Health," "Collective Oral Health" comprises, at one time, also the field of "Dentistry," attaching and redefining it, and, therefore, necessarily going beyond it [27–31].

The *Collective Oral Health* argues that the "oral health" amidst the population does not result solely from the dentistry practice, but from social constructions that men consciously carry out in each concrete situation – there included health professionals and also (or even…) dental surgeons. As a social process, each situation is unique, singular, historical, and thus cannot be mechanically replicated or reproduced in any other concrete situation, once the elements and dimensions of each one of those processes include contradictions, create conflicts, and are marked by negotiations and pacts of their own, specific. It intends to replace "[…] every form of *technicism* and *biologism* present in the specific formulations of the area traditionally known as Social and Preventive Dentistry or Public Health Dentistry. It searches to build the theoretical framework in an articulated and organic way concerning how the *Collective Health* conceives and acts, and reinforcing the historical commitment of the latter with the quality of life in the society and citizenship advocacy against both the predatory action of capital and the authoritarian action by the State." [32].

Scientific knowledge on the relation between systemic conditions, oral health, and quality of life has been growing over recent years. The conviction that managing chronic systemic conditions may not ignore dental care as part of overall healthcare is increasing, if the aim is to reach a quality level of healthcare compatible with the volume of current scientific evidence. Thus, in both the primary healthcare and actions of specialized and hospital-based care, the participation of the oral health team jointly with the multi-professional team may be considered an essential element of qualification of the healthcare provided by well-structured health systems. As part of the international political agenda of public health, the water fluoridation has been the subject of many studies discussing different aspects related to that practice. Aspects related to water sources, the extent of the water supply system, the acceptance by the population to use it, and the sharing of costs of both the treatment and the distribution, by the State and the society are themes that involve different sectors and political agents. Therefore, they engender serious disputes and debates about public policies of health and sanitation [33].

The *Collective Oral Health* recognizes that "oral health" of the population does not uniquely result from the dental practice, but rather from complex social processes that lead to physiological manifestations (good health conditions or injuries) in individuals who undergo particular experiences of good health and pain and suffering. This conception imposes on the *Collective Oral Health* an epistemological rupture with *Dentistry*, whose theoretical landmark is based on biological and individual aspects – on which its practice is grounded – ignoring in its doings the determination of "complex social processes."

In capitalism, the mode of production leads to what Narvai characterized as "Market Dentistry" [28], which is related to the process of changing health services into commodities, undermining health as a common good without exchanging value, and imposing to the healthcare market many ethical deformities widely known.

Therefore, epistemologically breaking up involves developing a *praxis* that must also break up, dialectically, with the hegemonic dental practice in the Western world. Such rupture requires the dental work to be developed based on the persons' needs (*all* persons), and that, opposing to the market logic, will break up with

the status quo fundamentally characterized by the "mercantilism" of services and the maintenance of the monopoly of access to dentistry resources (*all* resources) by those population segments which can afford them.

28.4 Theoretical Basis of the Influence of Social Policies on Population Oral Health and Inequalities

Macro-level factors, related to the economic and political context, have been identified as crucial determinants of population health and inequalities in various analyses and conceptual models [34–36]. Studies on the mechanisms underlying the distribution of health, including oral health, have shown that the social conditions in which people live are the main drivers. In turn, the distribution of those social conditions within a society is shaped by the political context [37]. Ultimately, politics determines which problems become priorities, and according to the priorities set, more or less robust economic/social policies will be designed and implemented.

The political context here refers to the structure or affairs of government, the State, public policies, power, and authority [38].

28.4.1 How Social Policies Affect Oral Health and Inequalities?

First, political decisions on social policies entirely affect the distribution of resources that are relevant to health, like education and nutrition [39]. In that way, those social policies could potentially impact not only the oral health of populations but also the relationship between socioeconomic characteristics and oral health. For example, events such as unemployment have adverse psychosocial effects including higher levels of stress and a lower sense of control over life, which in turn influence oral health through direct pathways (affecting the immune system) and indirectly given their influence on health behaviors [40]. These adverse effects would be somehow counterbalanced if universal and human rights-based benefits are provided as protection. Such protection is expected to enhance the sense of security and control (mostly among those in lower SEP) [41] which in turn would have positive effects on oral health.

In this discussion about the relationship between politics and health, it is important to explain some economic concepts briefly. In economics, different types of goods are defined based on the excludability and rivalrousness in their consumption. For example, the marginal cost of providing clean water and sanitation facilities (public goods) to an additional customer is practically zero and once supplied to a household; no extra cost exists in supplying them to others. In contrast, purchases of private goods, like an automobile or a piece of clothes, by one customer exclude others from obtaining it [42]. Contrary to public goods, private goods are excludable and rival. Most material resources relevant to population health are public goods, like electricity, clean water, sanitation facilities, education, healthcare, and security. Thus, the access to those resources in most societies depends not only on the individual income but also, above all, on the provision of these goods and services to citizens, which is determined by policies, institutions, and governance at multiple scales [43].

Another related way in which social policies could affect oral health is through dental care services. Social policies and political institutions determine how healthcare services in general and dental care services in particular are organized and reformed in different countries. Features of dental care systems, including coverage, funding, and the approach to provision, have been related to oral health and inequalities [44].

Finally, social policies and the social organization that they helped to create imply levels of interpersonal trust, sense of belonging, and social cohesion [45]. These public resources have the potential to benefit population health, including oral health [46, 47] and might influence how society approaches health inequalities.

Taking these potential pathways into consideration, oral health outcomes may vary according to political features in different societies. For example, social policies heavily influence the magnitude of inequalities in socioeconomic and living conditions. In turn, evidence has shown that practices of oral hygiene, diet, and use of dental care services are influenced by the socioeconomic circumstances and living conditions in which those behavioral choices are made [48, 49]. The pathway from social policies to psychosocial factors and the distribution of oral health has support in the literature. Societies whose policies prioritize the accumulation of private wealth over the redistribution of power and privilege exhibit higher levels of socioeconomic inequality and poorer health outcomes among those living and working in disadvantaged circumstances [50–52]. In different contexts, but particularly in those of deep social inequalities, people in lower socioeconomic positions experience more effort–reward imbalance at work, lower sense of coherence, and higher levels of chronic stress. These psychosocial factors play a significant role in explaining the distribution of oral health outcomes [53, 54].

The pathways mentioned above linking social policies and population oral health and inequalities can be summarized in the following figure, based on the Social Determinants of Health model from the Commission of

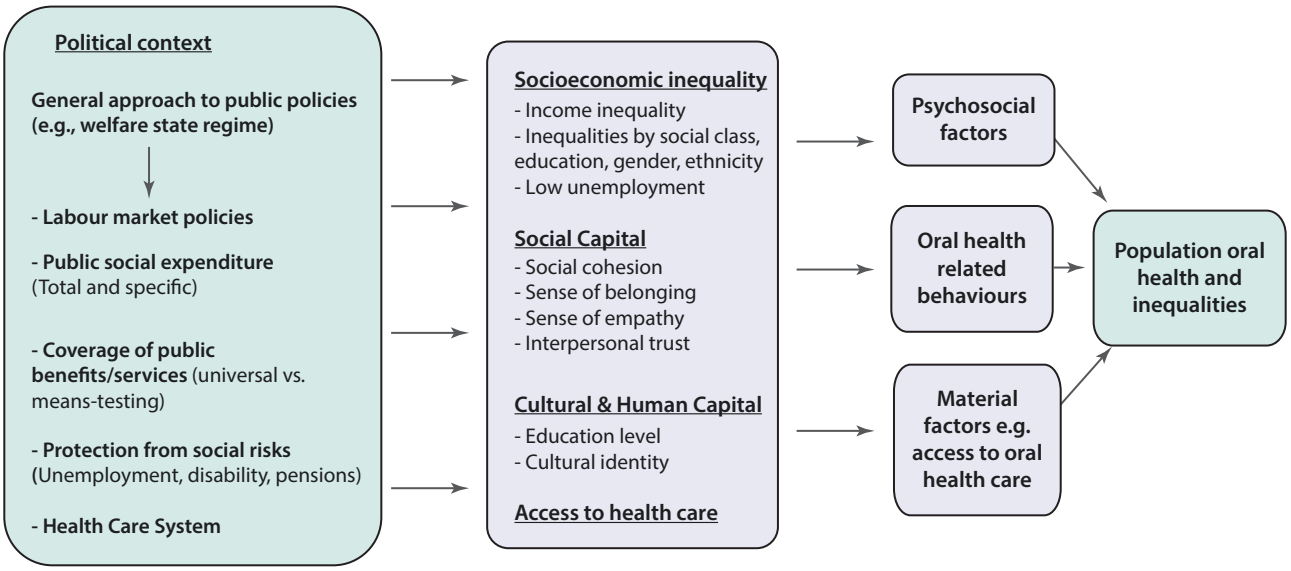


Fig. 28.1 A conceptual model for the impact of social policies on population oral health and inequalities. Based on the model of social determinants of health [36] and the model by Navarro and colleagues on the relationship between politics and health [34]

Social Determinants of Health [36] and the model by Navarro et al. [34], on the relationship between politics and health. The existence of these relationships means that the root causes of poor oral health and inequalities are in the socio-political structure, and more immediate determinants are politically and socially patterned (Fig. 28.1).

It is worth mentioning that other, more specific, policies such as those aiming to regulate access to sugars (including sweet beverages), cigarettes, and fluorides (using vehicles such as dentifrices, salt, and drinking water), also have the potential to affect oral health. Those will be discussed in the next section.

28.5 Evidence on the Relationship Between Social Policies and Population Oral Health (Including Inequalities)

In this section, we review some of the evidence on the relationship between social policies and population oral health, including inequalities. This evidence will be presented from general to specific, that is, first, we will focus on studies analyzing more general political factors; second, those on specific social policies (income support, healthcare, etc.); and, finally, more particular policies aimed to impact oral health (e.g., restriction to sugars and access to fluorides). It is important to clarify that this review is meant to be illustrative rather than comprehensive.

28.5.1 General Political Factors and Oral Health

Some studies have explored the potential role of general political factors such as governance, welfare state regimes, and general political changes on oral health and inequalities. Most of these analyses are based on cross-national comparisons given that these political factors are usually homogeneous within countries [55]. For example, a recent study examined different structural determinants of children's oral health in 11 countries and found that political regime (typology of democracy and dictatorship) and governance level (based on political stability, the rule of law, voice and accountability, etc.) were both associated with oral health-related quality of life – OHRQoL [56]. Better OHRQoL was observed in children living in parliamentary democracies and countries with higher governance levels compared to those living in dictatorships and countries with low governance. That analysis also showed that the type of welfare state regime was significantly related to both clinical oral health and OHRQoL. Welfare state regimes refer to groups of countries defined according to their general approach to social policies (housing, education, health, etc.) expressed in their welfare structure and institutions [57]. Since the 1990s, similarities and differences in the type and content of welfare policies have been used to cluster countries in diverse typologies of welfare state regimes.

> Welfare state refers to the role played by the state in the provision of social benefits and services including housing, education, health, and poverty relief, among others [38].

Additional work has examined the potential role of welfare state regimes as determinants of oral health and inequalities, mainly in European countries. Overall, that evidence suggests that oral health and regular dental attendance are significantly better in welfare states with more redistributive and universal welfare policies (Scandinavian/Social democratic) and poorer outcomes are observed in Eastern and Southern European regimes [52, 58, 59]. Improvements in population health in Scandinavian welfare states, including oral health, have been attributed to their strong redistributive social security system and their health policies with a large number of universal healthcare services and different strategies to explicitly target social determinants of health [60, 61]. Regarding inequalities, findings of comparative studies indicate that significant social gradients in oral health exist in all welfare regimes [62]. When the magnitude of inequalities is compared across regimes, there is no clear pattern, with different findings according to the outcome measure, SEP indicator, and welfare regime typology [62–64]. The fact that countries with the most redistributive and universal welfare policies, that is, those in the social-democratic or Scandinavian welfare regime, are not consistently exhibiting the lowest inequalities is also observed when analyzing general health outcomes in what has been called a public health "puzzle" or "paradox" [65, 66]. It is worth mentioning that, even though the overall magnitude of inequalities is not the lowest in Scandinavian states, those in the lower SEP levels are better off in terms of oral health there than in other welfare states [52].

Finally, as regards general political factors, some studies have examined the impact of broad political changes on oral health and inequalities. Two of them aimed at assessing the consequences of political changes implemented in the 1990s including reduction in welfare benefits and cuts in public spending. The first one used data from a cohort of Swedish adults and found no significant changes in the magnitude of oral health inequalities between 1992 and 1997 [67]. The authors stated that this occurred because the study period was not long enough to detect significant impacts of contextual changes. The second study showed an increase in ethnic inequalities in children's oral health in New Zealand from 1995 to 2000, with poorer outcomes for those of Maori and Pacific ethnic origin [68]. The study concluded that political changes in the early 1990s were detrimental to the health of people living in disadvantaged households. For this type of studies, it is essential to bear in mind that the study period required to assess changes in oral health after political changes is more extensive than for other health measures, particularly when examining non-reversible and cumulative outcomes like dental caries [69].

All this evidence together suggests that population oral health and inequalities are associated with general political factors, probably through the pathways described in the previous section. Further research is needed to explore the potential role of other general political factors, analyze these issues in different settings including more studies in low- and middle-income countries, and employ robust analytical tools such as difference-in-difference models and instrumental variables analysis.

28.5.2 Certain Specific Social Policies and Population Health

What about the evidence on the relationship between specific social policies and population health and inequalities? Whereas some studies have been conducted to examine this issue on general health outcomes, the evidence on oral health is still developing. Regarding the former, the healthcare policy (or healthcare system) is the social policy more frequently analyzed given its expected effect on population health. Better health outcomes and mainly lower health inequalities have been associated with certain characteristics of the healthcare systems. These include higher public health expenditure [70], universal coverage [71, 72], lower involvement of the private sector [73], less out-of-pocket spending [74, 75], equal access to quality services when required [74, 76], a primary care approach rather than prominence of specialist care [77–79], and development of inter-sectoral strategies [74, 75]. In contrast, total spending on healthcare alone does not appear to have a significant effect [80].

Another body of evidence has focused on the potential health impact of income support policies. In general, those policies aim to raise the financial resources available to beneficiaries and reduce income inequalities [81]. Studies on this area have explored whether the increase in available resources through supplementary income or cash transfers has had some impact on the health of their beneficiaries. To date, some of this evidence suggests that there could be such an effect. In the USA, for example, a study comparing the generosity of

unemployment benefit programs across states between 1968 and 2008 showed that some of the negative impact of unemployment on suicide was counterbalanced by the presence of generous benefits [82]. Also in the USA, an 11% reduction in the probability of disability was observed with a 15%–20% increase in income among elderly beneficiaries of a federal cash transfer program targeting very poor adults aged ≥65 years [83]. A similar finding, although larger in magnitude, was found in Mexico with the PROGRESA program. In that case, a 20% reduction in mobility limitations was identified among adults aged ≥50 years after a 20% increase in household income [84].

The Mexican PROGRESA/Oportunidades program and others of this type are called *conditional* cash transfer (CCT) programs because the cash transfers are conditional on the beneficiary families complying with certain conditions. Examples of those conditions include children and adolescents regularly attending school, household members having regular health check-ups, young children being taken to get vaccinated, and mothers attending information sessions on health and nutritional practices [85]. These CCT programs were initially implemented in middle-income countries in Latin America (Brazil and Mexico). Subsequently, they became increasingly popular in other regions: Asia, Africa, and North America. Research on the health effects of these programs has focused on children and adolescents, with specific findings showing positive impacts on early growth and childhood mortality, immunization coverage, the prevalence of overweight, reduced behavioral problems, and motor and cognitive development rates [86–88].

Despite the positive effects on health mentioned above, the evidence on the health benefits of income support policies is not entirely conclusive. Analyses evaluating the effects of the programs Aid to Families with Dependent Children and Earned Income Tax Credit in the USA have shown mixed findings regarding their impact on birthweight, obesity, and smoking [81]. Additionally, some of the studies on CCT programs found positive effects for some outcomes but non-significant for others [86, 87]. Moreover, in many studies, it is difficult to attribute to cash transfers the positive impacts on health because other components may also play a role. Given that income support policies target specific groups, usually those with very low income, it is also important to highlight that focusing only on the most disadvantaged within societies is not sufficient to comprehensively address the existing social gradients in health and their determinants. Tackling such pervasive gradients require social policies aimed at ensuring to all members of society opportunities, access to quality healthcare, safe living and working environments, and, in general, access to material and non-material resources that are important for health.

Before turning to studies focused on oral health, we should mention that particular features of some education policies have also been linked to population health outcomes. Interesting examples are the health benefits observed among participants of the Carolina Abecedarian Project (ABC) and the Perry Preschool Project (PPP) [89]. Both projects targeted disadvantaged children in their early childhood, included preschool curriculum changes, have been assessed using random assignment and have long-term follow-ups. In the ABC intervention, children were immersed in an intellectually stimulating environment during the first 5 years of their life, with a curriculum based on "learning games" which emphasize on language, emotional regulation, and cognitive skills. Participant children also received two meals and a snack at the childcare center and primary pediatric care. Health benefits of the ABC have been observed across different stages of the life course and include participants being more physically active at 20–25 years [90] and having a lower prevalence of risk factors for metabolic and cardiovascular diseases in their mid-30s [91]. The other early childhood program, the PPP, was implemented on children aged 3–5 years who were enrolled in pre-school activities based on active learning, "which is centred on play, based on problem-solving and placed within a structured daily routine" [89]. Although PPP did not have a nutritional and healthcare component like ABC, positive health effects have been observed, particularly on health-related behaviors, even 37 years after the intervention [92]. These findings and others from different studies have shown that investments in early childhood, educational experiences, in particular, are very relevant for health not only during the early years of life but throughout the life course [93]. The World Health Organization's Commission on Social Determinants of Health took this knowledge into account and stated that promoting a good start in life was a priority to achieve equity in health [36].

We have presented some examples of studies analyzing the potential health effects of certain features of healthcare, income, and education policies. There are, of course, other social policies or strategies with potential or demonstrated positive impacts on population general health. However, a thorough review of that evidence is out of the scope of this chapter.

As we mentioned before, studies about the impact of specific social policies on oral health are scarce. In one of the few analyses on this issue, a multilevel study evaluated the potential association between public policies, income inequality, and oral health among Brazilian 15- to 19-year-olds [94]. A scale of Municipal Public Policies was used by combining indicators of four policy areas: sanitation and infrastructure, child's welfare, education, and public dental services. The

study showed that public policies explained most of the income inequality effect on oral health. The analysis also revealed that policies had an independent, contextual effect on oral health that varied by SEP, with more substantial positive impacts for those with higher levels of education and income. In a similar, more recent analysis, the authors explored the potential impact of public policies on oral health across different household income levels [95]. This time, the policies were assessed separately rather than combined in a scale, with areas of education, sanitation, and dental services being considered. In addition, the provision of fluoridated drinking water was assessed. Findings showed that better oral health outcomes, particularly untreated caries and missing teeth, were associated with more favorable social policies and higher coverage of water fluoridation. Those associations were observed across income levels, and no significant difference in the magnitude of oral health inequalities was observed between municipalities with different policy development/coverage.

Findings of the two previous studies showed that public policies, which were not specifically aimed to impact oral health, can have a significant effect on population oral health outcomes and eventually reducing inequalities. Also, these oral health studies reported a positive impact of educational policies. They included policies on water fluoridation and dental care services, which explicitly aimed to impact oral health, but the next session will discuss these themes. Future research on this area should explore different social policies with the potential to affect oral health as well as mechanisms leading to oral health and inequalities. Assessing the potential role of behavioral, material, psychosocial, and social relational factors, and how they operate under different political contexts would shed light on this area of political determinants of oral health. This task, however, is not easy, given the methodological challenges in obtaining valid effect estimates and having good-quality data for this type of analysis.

28.5.3 Particular Policies Aimed to Impact Oral Health

Policies aimed to impact oral health include those related to dental care services and initiatives directed to increase the access to fluoride. This section briefly discusses this topic. We will also refer to policies aimed to reduce consumption of sugary foods and drinks, although they are not exclusively or primarily designed to affect oral health.

The provision of dental care is often a matter of policy debate, with many countries having separate policies for general health and oral health services. Even in countries with universal healthcare, oral health services are, almost entirely, privately financed and provided with high out-of-pocket expenses [44]. Although evidence has suggested that dental care may have relatively little impact on population oral health and inequalities compared to other determinants [96], it seems that the approach to provision, services coverage, and type of funding may still have a role to play. For example, a recent systematic review on socioeconomic inequalities in dental caries concluded that inequalities were steeper in high-income countries, and suggested that the approach to dental care in those countries, mainly focused on restorative treatments, may play a role in explaining the observed inequalities [97].

The potential impact of an oral health policy based on universal coverage and a primary care approach, implemented in Brazil, has been considered in a group of studies [69, 98, 99]. With the creation of the Brazilian Unified National Health System, the "Sistema Único de Saúde" (SUS), the number of municipalities without dental care resources decreased, and school dental clinics were transferred to the primary healthcare network, thereby creating the conditions for greater integration between dental care activities and other programs. From 2004, the dental care strategy has been part of a broader national oral health policy, called Smiling Brazil "Brasil Sorridente" within the SUS. Crucially, oral health was selected as one of the four priority areas of the SUS [98]. Besides aiming to guarantee universal access to dental care with a primary care approach, the Smiling Brazil policy involved robust epidemiological oral health surveillance and community-based prevention programs and, mainly, supervised toothbrushing with fluoride toothpaste in schools and water fluoridation. Nationally representative data have shown a significant decline in the most prevalent oral diseases. For dental caries, the decline mostly affected children and adolescents, and it occurred after the implementation of the Smiling Brazil policy [69, 98, 99].

Moreover, a review of evidence on this topic and other studies showed that the dental care public policy was also associated with a reduction in inequalities, for example, in accessing services when needed, even though it was still in expansion and had not yet achieved comprehensive and universal coverage [100, 101]. Later analysis revealed, however, that inequalities in specific oral health outcomes did not significantly declined during the period following the policy implementation, or stop decreasing after 2008 [69, 102]. Although the oral health of adults has not improved as quickly as that of younger Brazilians and the results on inequalities are still unclear, the example of this policy suggests that universal, primary care oriented and publicly funded oral health services might have relevant benefits for population oral health.

The positive impact of public funding and universal coverage of oral health services has also been identified in studies of high-income countries. In a comparison of 11 European countries, authors found that educational inequalities in the use of dental care services were higher in countries with no provision of public dental care than in countries where oral health services were covered, to some degree, by the public health system [44]. Other analyses have examined inequalities in the use of health services in Spain and established that dental care, the only service not covered by the public system, exhibited the highest inequalities [103, 104]. Additionally, a study reported that income inequalities in accessing oral health services were pervasive in a context of privately financed dental care (Canada), and were even larger for preventive care than for other types of dental services [105]. Evidence also suggests that in addition to public funding and universal coverage, the scope of the benefits should be sufficient to impact inequalities, as reported in Thailand [106].

In 2007, for the first time in 25 years, oral health was subject to discussion by the World Health Assembly and the Executive Board of WHO. The Member States agreed on an action plan for oral health and integrated disease prevention, including activities for raising awareness of the determinants of oral and general health, fostering health-promoting environments, healthy behavior, and prevention-oriented oral health systems. In this context, it is also important to mention that Universal Health Coverage (UHC) has been increasingly recognized as a policy priority and one of the key strategies needed to achieve global health goals and reduce health inequalities [107, 108]. Authors in the oral health field have acknowledged this global movement for UHC as a strategic opportunity " to ensure that oral health is recognized as a key public health priority and is integrated into the UHC policy agenda" [107].

> Universal Health Coverage (UHC): "ensuring that all people can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship" [107, 109].

Besides dental care services, perhaps the most studied policies/strategies in oral health are those aimed to increase access to fluorides [110] and among them, water fluoridation. American specialists included it among the ten most important public health achievements of the twentieth century [111], and there is strong evidence of its benefits for prevention of dental caries, particularly for children and previous to the massive introduction of fluoride toothpaste [112, 113]. There has been some controversy, however, about its benefits in subsequent years due to the scarcity of more recent analyses [112, 113]. Most contemporary studies follow a design in which fluoridated and non-fluoridated communities are compared, but with no pre-fluoridation data – limiting to some extent the strength of their evidence [112]. Despite this limitation, more recent evidence has incorporated methodological improvements like adjustments for potential confounders and assessment of the time living in areas with access to fluoridated water [95, 113, 114]. Findings of this contemporary evidence continue to indicate that positive impacts on caries levels exist, even among adults [115]. In terms of economic evaluations, recent evidence points toward a consistent economic benefit of water fluoridation that exceeds the intervention cost. This benefit–cost ratio seems to rise with the community population size [116, 117].

In terms of the effects of water fluoridation on oral health inequalities, although the evidence is still insufficient to give a definitive answer, some studies suggest that it may contribute to decreasing differences in caries levels across socioeconomic groups. For example, a recent analysis of Australian data for children aged 5–14 years found that water fluoridation contributed to reducing absolute income inequalities in caries experience in both deciduous and permanent teeth [118]. However, other studies have shown that water fluoridation does not seem to be enough to close the gap in the dental caries burden between socioeconomic and ethnic groups [100, 119]. In Brazil, studies have shown that the coverage of water fluoridation tends to be higher in larger municipalities and in those with a higher level of human development [120]. This pattern is an example of the "inverse equity hypothesis," which states that universal public health interventions might initially benefit more groups in higher socioeconomic positions, thus increasing inequalities in early stages of implementation [121]. In line with this hypothesis and taking into account findings of a recent study which showed a reduction in municipal inequality in access to water fluoridation in Brazil since 2000 [120], one would expect a more significant impact on caries inequalities in the years to come. The evidence available to date seems to suggest that water fluoridation must have universal geographical coverage to have a positive impact on inequalities. Also, it must be accompanied by strategies/policies aimed to affect other complex and diverse determinants of oral health inequalities.

Other strategies of acknowledged safety and effectiveness for increasing access to fluorides make use of cooking salt and dentifrice as vehicles. Studies on effects of salt fluoridation have shown results similar to those observed after the introduction of water fluoridation, given support to the idea that it should be considered as

a practical alternative wherever water fluoridation is not socially acceptable or feasible [122]. Regarding fluoride toothpaste, in some regions of the world, this is the only viable strategy to control tooth decay at the population level, because the lack of financial or technological resources prevents cheaper alternatives such as water or salt fluoridation. However, fluoride toothpaste is not equally accessible among high-, middle-, and low-income countries [123] and even among families from different socioeconomic strata within the same country. Differences in accessibility to fluoride toothpaste can contribute to inequalities in the distribution of caries [110]. School-based toothbrushing programs are broadly recommended for assuring access of children and adolescents to fluoride. Also, efforts should be made to develop affordable fluoride toothpaste, exempting them from duties and taxation applied to cosmetics [122, 124].

In this chapter, we have not reviewed oral health policies using other preventive strategies, though there is a growing body of evidence on such issues. As an example, in the U.S., some states included in their Medicaid policies, the application of fluoride varnish by primary care dental providers. A comparison between states with and without such guideline showed that oral health for publicly insured children was better where the policies had been introduced [125].

As a final point in this section, we refer to some evidence on policies aimed to reduce the consumption of sugary foods and drinks. The increasing availability of this type of products is responsible for a large proportion of dental caries, obesity, and non-communicable diseases worldwide. Moreover, it is considered the main cause of the increasing caries prevalence during recent decades in various low-income countries [126]. Policies aimed at reducing the consumption of sugary foods and drinks can have a significant impact on population oral health. Moreover, since the consumption is usually higher among lower socioeconomic strata, these policies can also contribute to decreasing inequalities in oral health. Policies in this area include fiscal measures like the "sugar taxes" and restrictions to marketing and advertisement. Implementing such policies, however, is challenging given the economic interests of the food industry and the power they exert through different strategies in the so-called corporate and commercial determinants of health [127].

Recent evidence has shown that taxes reduced the consumption of sugary drinks in different settings where such policies have been enacted, including high- and middle-income countries [128, 129]. Furthermore, change in consumption seems to be more significant among lower income groups, with a potentially positive impact on health inequalities. In general, changes in food/drinks consumption appear to be higher after price policies or those with a multi-component base, compared with those based only on food labeling or restrictions on provision or marketing [130]. Regarding the impact of a sugar-sweetened beverage tax on oral health, an economic simulation using German data revealed that a 20% tax would significantly reduce caries increment and treatment costs, particularly among low-income young male adults [131]. The sugar tax could contribute to reducing inequalities in caries experience. Positive impacts on population caries levels were also found in similar analyses using Australian [132] and UK data [133]. It is important to highlight that authors in this field have stated that policies to reduce consumption of sugary foods and drinks should be part of a broader policy strategy to guarantee access to affordable, healthy food for all members of society [126, 134].

28.6 Conclusion

Finally, some concluding remarks are necessary. The study of political determinants of health is a challenging endeavor which requires many studies providing the best possible evidence from different settings and using complementary theoretical perspectives and analytical approaches. High-quality research is needed to enhance our understanding of the potential role of different social policies as macro-level determinants of population oral health and inequalities. Research should explore the role of political factors at different levels: (1) general political factors, such as different political and economic regimes (welfare, democracies, and autocracies, etc.) and governance patterns; (2) specific public policies like conditional cash transfer programs, sanitation, education, and healthcare; and (3) more particular policies aimed to impact oral health (e.g., water fluoridation). This area of the political determinants of oral health and patterns of inequalities would also benefit from considering different moments of the life course, ideally using longitudinal data and analyzing specific subpopulation groups. In addition, the mechanisms (pathways) through which those policies affect oral health and how they operate under different contexts should also be a matter of future analyses. The study of these issues would enhance our capacity to appropriately inform national and cross-national strategies and move from actions focused on factors at the individual level, such as behaviors, to more structural interventions, which would have a higher population impact and would be more effective in reducing health inequalities.

Policy arrangements to tackle the persistent oral health problems and inequalities should also involve changes in the provision and training of dental personnel, including dentists and middle-level workers. We think that some basic concepts about power and public policies as well as how they relate to the fields of epidemiology and public health should be part of the health

professionals' curriculum, including dentists. It would also be useful to include some discussions (using a historical lens) about the politics behind both research studies and the way health issues have been understood and addressed.

We are aligned with those who think that research and academic training should follow sustained actions of advocacy and social mobilization. To face the challenges of Public Health in the twenty-first century, experts have emphasized the need for political engagement in public health practices [135]. "*According to them, the neglect of the political dimension of health has been provoked by the predominance of biomedical thinking and conservative and neoliberal ideology, including the effect of health sector reforms under its aegis. In addition, insufficient attention is paid to training programs and lines of research on the determinants of health policies and effective programs, corroborated by the power of commercial interests and lack of trust and courage of many professionals, which have also contributed to this picture*" [136]. As the inequality crisis continues to worsen worldwide, and the benefits of economic growth continue to concentrate in fewer hands, dentistry remains (under market imperatives) not developed based on people's needs – with the more visible effect being the maintenance of a monopoly of access to dentistry resources by those population segments which can afford them.

Oral health still has a relatively low political priority [137], and the underlying determinants of oral problems and inequalities are in many cases unknown to the communities and ignored by policymakers. Useful for advocacy purposes are analyses of the processes behind the policies, including the role of different stakeholders and the principles/interests behind the decisions made. This kind of studies together with those mentioned above would allow researchers to put evidence to the service of social organization with the aim to benefit population health through emancipation and social justice.

Points of Emphasis/Importance

- The practice of epidemiology produces scientific knowledge that carries strategic value and raises interest among social groups that assign political relevance to that knowledge.
- To fully understand the underlying causes of health (oral health) problems, epidemiology should consider the political situation and the way power is practiced, including the role of State institutions, non-governmental organizations, private groups, and social movements.
- A new Public Health/Dental Public Health approach argues that if economic and social determinants are the main factors behind population health issues, economic and social policies should be the measures to challenge them.
- Those economic and social policies can affect oral health through the distribution of critical resources like education, nutrition, and dental care services.
- Evidence suggests that population oral health and inequalities are associated with general political factors such as governance and welfare state regimes. Studies on the relationship between specific social policies and oral health are very scarce, while for general health some studies point toward the potential effects of specific healthcare, income, and education policies.
- Policies on dental care services, access to fluorides, and consumption of sugary foods and drinks have also shown to have potential effects on oral health.

References

1. Castells M. The rise of the network society. The information age: economy, society, and culture. Volume I. Oxford: Wiley-Blackwell; 1997.
2. Seymour B, Getman R, Saraf A, Zhang LH, Kalenderian E. When advocacy obscures accuracy online: digital pandemics of public health misinformation through an antifluoride case study. Am J Public Health. 2015;105(3):517–23.
3. Last JM. A dictionary of epidemiology. 2nd ed. New York: Oxford University Press; 1988.
4. Carvalho DM. Epidemiologia, história e fundamentos. In: Medronho R, editor. Epidemiologia. São Paulo: Atheneu; 2003. p. 3–14.
5. Terris M. La revolución epidemiológica y la medicina social. Siglo XXI: México; 1980.
6. Foucault M. Microfísica do poder. 8th ed. Rio de Janeiro: Edições Graal; 1989.
7. Almeida-Filho N. Epidemiologia sem números: uma introdução crítica à ciência epidemiológica. Rio de Janeiro: Campus/Abrasco; 1989.
8. Barreto ML, De Almeida-Filho N, Breilh J. Epidemiology is more than discourse: critical thoughts from Latin America. J Epidemiol Community Health. 2001;55(3):158–9.
9. Rose G. The strategy of preventive medicine. Oxford: Oxford University Press; 1992.
10. Berlinguer G. Medicina e política. CEBES-Hucitec: São Paulo; 1978.
11. Berlinguer G. A doença. CEBES-Hucitec: São Paulo; 1988.
12. Snow J. On the mode of transmission of cholera. London: Churchill; 1855.
13. Rosen G. A history of public health. New York: MD Publications; 1958.
14. Illich I. Medical nemesis: the expropriation of health. London: Calder & Boyars; 1975.
15. Ferreira JR. La crisis. In: Organización Panamericana de la Salud, editor. La crisis de la salud pública: reflexiones para el debate. Washington, D.C.: (OPS - Publicación Científica, 540); 1992. p. 233–6.
16. Lalonde M. A new perspective on the health of Canadians. A working document. Government of Canada: Ottawa; 1974.
17. Ashton J, Seymour H. The new public health: the Liverpool experience. Milton Keynes: Open University Press; 1988.
18. MacDougall H. Reinventing public health: a new perspective on the health of Canadians and its international impact. J Epidemiol Community Health. 2007;61(11):955–9.

19. Awofeso N. What's new about the "new public health"? Am J Public Health. 2004;94(5):705–9.
20. Frazão P, Minakawa MM. Medicalização, desmedicalização, políticas públicas e democracia sob o capitalismo. Trabalho, Educação e Saúde. 2018;16(2):407–30.
21. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14(1):32–8.
22. Paim JS, de Almeida Filho N. Collective health: a "new public health" or field open to new paradigms? Rev Saude Publica. 1998;32(4):299–316.
23. Paim J. Collective health and the challenges of practice. In: Organización Panamericana de la Salud, editor. La crisis de la salud pública: reflexiones para el debate. Washington, D.C.: (OPS - Publicación Cientifica, 540); 1992.
24. Vieira-da-Silva LM, Pinell P. The genesis of collective health in Brazil. Sociol Health Illn. 2014;36(3):432–46.
25. Petersen PE. Global policy for improvement of oral health in the 21st century--implications to oral health research of World Health Assembly 2007, World Health Organization. Community Dent Oral Epidemiol. 2009;37(1):1–8.
26. Exley C. Bridging a gap: the (lack of a) sociology of oral health and healthcare. Sociol Health Illn. 2009;31(7):1093–108.
27. Botazzo C, Manfredini MA, Narvai PC, Frazao P. Saúde bucal coletiva. Instituto de Saúde: Sao Paulo; 1988.
28. Narvai PC. Odontologia e saúde bucal coletiva. Hucitec: São Paulo; 1994.
29. Cordon J. Building an agenda for collective oral health. Cad Saude Publica. 1997;13(3):557–63.
30. Moysés SJ. O conceito de promoção da saúde na construção de sistemas de atenção em saúde bucal coletiva. In: Kriger L, editor. Promoção de saúde bucal. São Paulo: ABOPREV-Artes Médicas; 1997. p. 371–407.
31. Frazao P. Tecnologias em saúde bucal coletiva. In: Botazzo C, Freitas S, editors. Ciências sociais e saúde bucal: questões e perspectivas. Bauru e São Paulo: Edusc-Ed.Unesp; 1998. p. 159–74.
32. Narvai PC, Frazão P. Saúde bucal no Brasil: muito além do céu da boca. Rio de Janeiro: Editora Fiocruz; 2008.
33. Frazão P. Posfácio. In: Chaves SCL, editor. Política de saúde bucal no Brasil. Salvador: Editora da Universidade Federal da Bahia; 2016.
34. Navarro V, Muntaner C, Borrell C, Benach J, Quiroga A, Rodriguez-Sanz M, et al. Politics and health outcomes. Lancet. 2006;368:1033–7.
35. Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. Int J Epidemiol. 2001;30(4):668–77.
36. World Health Organization. Closing the gap in a generation: health equity through action on the social determinants of health: final report of the Commission on Social Determinants of Health. Geneva; 2008. 246 p.
37. Brennenstuhl S, Quesnel-Vallée A, McDonough P. Welfare regimes, population health and health inequalities: a research synthesis. J Epidemiol Community Health. 2012;66(5): 397–409.
38. Bambra C, Fox D, Scott-Samuel A. A politics of health glossary. J Epidemiol Community Health. 2007;61(7):571–4.
39. Borrell C, Espelt A, Rodriguez-Sanz M, Navarro V. Politics and health. J Epidemiol Community Health. 2007;61(8):658–9.
40. Sheiham A, Nicolau B. Evaluation of social and psychological factors in periodontal disease. Periodontol 2000. 2005;39: 118–31.
41. Dahl E, Fritzell J, Lahelma E, Martikainen P, Kunst AE, Mackenbach JP. Welfare state regimes and health inequalities. In: Siegrist J, Marmot MG, editors. Social inequalities in health: new evidence and policy implications. Oxford; New York: Oxford University Press; 2006. p. 193–221.
42. Howlett M, Ramesh M, Perl A. Studying public policy: policy cycles and policy subsystems. 3rd ed. New York: Oxford University Press; 2009.
43. Sellers JM, Arretche M, Kubler D, Razin E, editors. Inequality and governance in the metropolis: place equality regimes and fiscal choices in eleven countries. London: Palgrave Macmillan; 2017. p. 1–278.
44. Palencia L, Espelt A, Cornejo-Ovalle M, Borrell C. Socioeconomic inequalities in the use of dental care services in Europe: what is the role of public coverage? Community Dent Oral Epidemiol. 2014;42(2):97–105.
45. Martikainen P, Lahelma E, Marmot M, Sekine M, Nishi N, Kagamimori S. A comparison of socioeconomic differences in physical functioning and perceived health among male and female employees in Britain, Finland and Japan. Soc Sci Med. 2004;59(6):1287–95.
46. Kim D, Baum CF, Ganz ML, Subramanian SV, Kawachi I. The contextual effects of social capital on health: a cross-national instrumental variable analysis. Soc Sci Med. 2011;73(12): 1689–97.
47. Koyama S, Aida J, Saito M, Kondo N, Sato Y, Matsuyama Y, et al. Community social capital and tooth loss in Japanese older people: a longitudinal cohort study. BMJ Open. 2016; 6(4):e010768.
48. Chaves SCL, Vieira-da-Silva LM. Inequalities in oral health practices and social space: an exploratory qualitative study. Health Policy. 2008;86(1):119–28.
49. Jung S-H, Tsakos G, Sheiham A, Ryu J-I, Watt RG. Socio-economic status and oral health-related behaviours in Korean adolescents. Soc Sci Med. 2010;70(11):1780–8.
50. Krieger N, Alegria M, Almeida-Filho N, Barbosa da Silva J, Barreto ML, Beckfield J, et al. Who, and what, causes health inequities? Reflections on emerging debates from an exploratory Latin American/North American workshop. J Epidemiol Community Health. 2010;64(9):747–9.
51. Birn AE. Making it politic (al): closing the gap in a generation: health equity through action on the social determinants of health. Soc Med. 2009;4(3):166–82.
52. Guarnizo-Herreno CC, Watt RG, Stafford M, Sheiham A, Tsakos G. Do welfare regimes matter for oral health? A multilevel analysis of European countries. Health Place. 2017; 46:65–72.
53. Locker D. Self-esteem and socioeconomic disparities in self-perceived oral health. J Public Health Dent. 2009;69(1):1–8.
54. Sabbah W, Gomaa N, Gireesh A. Stress, allostatic load, and periodontal diseases. Periodontol 2000. 2018;78(1):154–61.
55. Muntaner C, Borrell C, Ng E, Chung H, Espelt A, Rodriguez-Sanz M, et al. Politics, welfare regimes, and population health: controversies and evidence. Sociol Health Illn. 2011;33(6): 946–64.
56. Baker SR, Foster Page L, Thomson WM, Broomhead T, Bekes K, Benson PE, et al. Structural determinants and children's oral health: a cross-national study. J Dent Res. 2018;97(10): 1129–36.
57. Bergqvist K, Yngwe MA, Lundberg O. Understanding the role of welfare state characteristics for health and inequalities -an analytical review. BMC Public Health. 2013;13:1234.
58. Guarnizo-Herreno CC, Tsakos G, Sheiham A, Watt RG. Oral health and welfare state regimes: a cross-national analysis of European countries. Eur J Oral Sci. 2013;121(3 Pt 1):169–75.
59. Listl S, Moeller J, Manski R. A multi-country comparison of reasons for dental non-attendance. Eur J Oral Sci. 2014;122(1):62–9.
60. Marmot M, Allen J, Bell R, Goldblatt P. Building of the global movement for health equity: from Santiago to Rio and beyond. Lancet. 2012;379(9811):181–8.

61. Bambra C. Cash versus services: 'Worlds of welfare' and the decommodification of cash benefits and health care services. J Soc Policy. 2005;34(2):195–213.
62. Guarnizo-Herreno CC, Watt RG, Pikhart H, Sheiham A, Tsakos G. Socioeconomic inequalities in oral health in different European welfare state regimes. J Epidemiol Community Health. 2013;67(9):728–35.
63. Sanders AE, Slade GD, John MT, Steele JG, Suominen-Taipale AL, Lahti S, et al. A cross-national comparison of income gradients in oral health quality of life in four welfare states: application of the Korpi and Palme typology. J Epidemiol Community Health. 2009;63(7):569–74.
64. Guarnizo-Herreno CC, Watt RG, Pikhart H, Sheiham A, Tsakos G. Inequalities in oral impacts and welfare regimes: analysis of 21 European countries. Community Dent Oral Epidemiol. 2014;42(6):517–25.
65. Bambra C. Health inequalities and welfare state regimes: theoretical insights on a public health 'puzzle'. J Epidemiol Community Health. 2011;65(9):740–5.
66. Mackenbach JP. The persistence of health inequalities in modern welfare states: the explanation of a paradox. Soc Sci Med. 2012;75(4):761–9.
67. Stahlnacke K, Soderfeldt B, Unell L, Halling A, Axtelius B. Perceived oral health: changes over 5 years in one Swedish age-cohort. Community Dent Oral Epidemiol. 2003;31(4):292–9.
68. Thomson WM, Williams SM, Dennison PJ, Peacock DW. Were NZ's structural changes to the welfare state in the early 1990s associated with a measurable increase in oral health inequalities among children? Aust N Z J Public Health. 2002;26(6):525–30.
69. Roncalli AG, Sheiham A, Tsakos G, Watt RG. Socially unequal improvements in dental caries levels in Brazilian adolescents between 2003 and 2010. Community Dent Oral Epidemiol. 2015;43(4):317–24.
70. Houweling TAJ, Caspar AEK, Looman WN, Mackenbach JP. Determinants of under-5 mortality among the poor and the rich: a cross-national analysis of 43 developing countries. Int J Epidemiol. 2005;34(6):1257–65.
71. Kunitz SJ, Pesis-Katz I. Mortality of white Americans, African Americans, and Canadians: the causes and consequences for health of welfare state institutions and policies. Milbank Q. 2005;83(1):5–39.
72. Mackenbach JP, Stirbu I, Roskam A-JR, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med. 2008;358(23):2468–81.
73. Benach J, Malmusi D, Yasui Y, Martinez JM, Muntaner C. Beyond Rose's strategies: a typology of scenarios of policy impact on population health and health inequalities. Int J Health Serv. 2011;41(1):1–9.
74. Mackenbach JP. An analysis of the role of health care in reducing socioeconomic inequalities in health: the case of the Netherlands. Int J Health Serv. 2003;33(3):523–41.
75. Gilson L, Doherty J, Loewenson R, Francis V. Challenging Inequity through Health Systems. Final Report Knowledge Network on Health Systems. WHO Commission on the Social Determinants of Health; 2007.
76. Wamala S, Merlo J, Bostrom G. Inequity in access to dental care services explains current socioeconomic disparities in oral health: the Swedish National Surveys of Public Health 2004-2005. J Epidemiol Community Health. 2006;60(12):1027–33.
77. Macinko JA, Shi L, Starfield B. Wage inequality, the health system, and infant mortality in wealthy industrialized countries, 1970-1996. Soc Sci Med. 2004;58(2):279–92.
78. Mosquera PA, Hernández J, Vega R, Martínez J, Labonte R, Sanders D, et al. The impact of primary healthcare in reducing inequalities in child health outcomes, Bogotá – Colombia: an ecological analysis. Int J Equity Health. 2012;11(1):66.
79. Macinko J, de Oliveira VB, Turci MA, Guanais FC, Bonolo PF, Lima-Costa MF. The influence of primary care and hospital supply on ambulatory care-sensitive hospitalizations among adults in Brazil, 1999-2007. Am J Public Health. 2011;101(10):1963–70.
80. Siddiqi A, Hertzman C. Towards an epidemiological understanding of the effects of long-term institutional changes on population health: a case study of Canada versus the USA. Soc Sci Med. 2007;64(3):589–603.
81. Glymour MM. Policies as tools for research and translation in social epidemiology. In: Social epidemiology. Oxford: Oxford University Press; 2014. p. 452–77.
82. Cylus J, Glymour MM, Avendano M. Do generous unemployment benefit programs reduce suicide rates? A state fixed-effect analysis covering 1968-2008. Am J Epidemiol. 2014;180(1):45–52.
83. Herd P, Schoeni RF, House JS. Upstream solutions: does the supplemental security income program reduce disability in the elderly? Milbank Q. 2008;86(1):5–45.
84. Gertler P. Final report: the impact of PROGRESA on health, vol. 2000. Washington, D.C.: International Food Policy Research Institute; 2000.
85. Behrman JR, Parker SW. Is health of the aging improved by conditional cash transfer programs? Evidence from Mexico. Demography. 2013;50(4):1363–86.
86. Ranganathan M, Lagarde M. Promoting healthy behaviours and improving health outcomes in low and middle income countries: a review of the impact of conditional cash transfer programmes. Prev Med. 2012;55:S95–S105.
87. Fernald LCH, Gertler PJ, Neufeld LM. 10-year effect of Oportunidades, Mexico's conditional cash transfer programme, on child growth, cognition, language, and behaviour: a longitudinal follow-up study. Lancet. 2009;374(9706):1997–2005.
88. Rasella D, Aquino R, Santos CA, Paes-Sousa R, Barreto ML. Effect of a conditional cash transfer programme on childhood mortality: a nationwide analysis of Brazilian municipalities. Lancet. 2013;382(9886):57–64.
89. Conti G, Heckman JJ. The developmental approach to child and adult health. Pediatrics. 2013;131(Suppl 2):S133–41.
90. Campbell FA, Wasik BH, Pungello E, Burchinal M, Barbarin O, Kainz K, et al. Young adult outcomes of the abecedarian and CARE early childhood educational interventions. Early Child Res Q. 2008;23(4):452–66.
91. Campbell F, Conti G, Heckman JJ, Moon SH, Pinto R, Pungello E, et al. Early childhood investments substantially boost adult health. Science. 2014;343(6178):1478–85.
92. Muennig P, Schweinhart L, Montie J, Neidell M. Effects of a prekindergarten educational intervention on adult health: 37-year follow-up results of a randomized controlled trial. Am J Public Health. 2009;99(8):1431–7.
93. Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet. 2017;389(10064):77–90.
94. Celeste RK, Nadanovsky P. How much of the income inequality effect can be explained by public policy? Evidence from oral health in Brazil. Health Policy. 2010;97(2–3):250–8.
95. Aguiar V, Pattussi MP, Celeste RK. The role of municipal public policies in oral health socioeconomic inequalities in Brazil: a multilevel study. Community Dent Oral Epidemiol. 2018;46(3):245–50.

96. Nadanovsky P, Sheiham A. Relative contribution of dental services to the changes in caries levels of 12-year-old children in 18 industrialized countries in the 1970s and early 1980s. Community Dent Oral Epidemiol. 1995;23(6):331–9.
97. Schwendicke F, Dorfer CE, Schlattmann P, Page LF, Thomson WM, Paris S. Socioeconomic inequality and caries: a systematic review and meta-analysis. J Dent Res. 2015;94(1):10–8.
98. Pucca GA, Gabriel M, de Araujo ME, de Almeida FCS. Ten years of a national oral health policy in Brazil: innovation, boldness, and numerous challenges. J Dent Res. 2015;94(10):1333–7.
99. Peres MA, Barbato PR, Reis SC, Freitas CH, Antunes JL. Tooth loss in Brazil: analysis of the 2010 Brazilian Oral Health Survey. Rev Saude Publica. 2013;47(Suppl 3): 78–89.
100. Antunes JLF, Narvai PC. Dental health policies in Brazil and their impact on health inequalities. Rev Saude Publica. 2010;44(2):360–5.
101. Peres KG, Peres MA, Boing AF, Bertoldi AD, Bastos JL, Barros AJ. Reduction of social inequalities in utilization of dental care in Brazil from 1998 to 2008. Rev Saude Publica. 2012;46(2):250–8.
102. Mullachery P, Silver D, Macinko J. Changes in health care inequity in Brazil between 2008 and 2013. Int J Equity Health. 2016;15(1):140.
103. Palencia L, Espelt A, Rodriguez-Sanz M, Rocha KB, Pasarin MI, Borrell C. Trends in social class inequalities in the use of health care services within the Spanish National Health System, 1993–2006. Eur J Health Econ. 2013;14(2):211–9.
104. Garrido-Cumbrera M, Borrell C, Palencia L, Espelt A, Rodriguez-Sanz M, Pasarin MI, et al. Social class inequalities in the utilization of health care and preventive services in Spain, a country with a national health system. Int J Health Serv. 2010;40(3):525–42.
105. Grignon M, Hurley J, Wang L, Allin S. Inequity in a market-based health system: evidence from Canada's dental sector. Health Policy. 2010;98(1):81–90.
106. Somkotra T, Detsomboonrat P. Is there equity in oral healthcare utilization: experience after achieving universal coverage. Community Dent Oral Epidemiol. 2009;37(1):85–96.
107. Mathur MR, Williams DM, Reddy KS, Watt RG. Universal health coverage: a unique policy opportunity for oral health. J Dent Res. 2015;94(3 Suppl):3s–5s.
108. Fisher J, Selikowitz HS, Mathur M, Varenne B. Strengthening oral health for universal health coverage. Lancet. 2018;392(10151):899–901.
109. World Health Organization. World Health Report, 2010: health systems financing the path to universal coverage. 2010.
110. Jones S, Burt BA, Petersen PE, Lennon MA. The effective use of fluorides in public health. Bull World Health Organ. 2005;83(9):670–6.
111. Centers for Disease Control and Prevention. Achievements in public health, 1900–1999: fluoridation of drinking water to prevent dental caries. MMWR. 1999;48:933–40.
112. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, et al. Water fluoridation for the prevention of dental caries. Cochrane Database Syst Rev. 2015;(6):Cd010856.
113. Rugg-Gunn AJ, Do L. Effectiveness of water fluoridation in caries prevention. Community Dent Oral Epidemiol. 2012;40(Suppl 2):55–64.
114. Slade GD, Grider WB, Maas WR, Sanders AE. Water fluoridation and dental caries in U.S. children and adolescents. J Dent Res. 2018;97(10):1122–8.
115. Peres MA, Peres KG, Barbato PR, Hofelmann DA. Access to fluoridated water and adult dental caries: a natural experiment. J Dent Res. 2016;95(8):868–74.
116. Ran T, Chattopadhyay SK. Economic evaluation of community water fluoridation: a community guide systematic review. Am J Prev Med. 2016;50(6):790–6.
117. Moore D, Poynton M, Broadbent JM, Thomson WM. The costs and benefits of water fluoridation in NZ. BMC Oral Health. 2017;17(1):134.
118. Spencer J, Do L, Ha D. Fluoride and oral health inequalities; childhood caries. In: Peres M, Watt RG, editors. Policy solutions for oral health inequalities. Melbourne: International Centre for Oral Health Inequalities Research and Policy; 2017.
119. Lalloo R, Jamieson LM, Ha D, Ellershaw A, Luzzi L. Does fluoride in the water close the dental caries gap between indigenous and non-indigenous children? Aust Dent J. 2015;60(3):390–6.
120. Frazao P, Narvai PC. Water fluoridation in Brazilian cities at the first decade of the 21st century. Rev Saude Publica. 2017;51:47.
121. Victora CG, Vaughan JP, Barros FC, Silva AC, Tomasi E. Explaining trends in inequities: evidence from Brazilian child health studies. Lancet. 2000;356(9235):1093–8.
122. O'Mullane DM, Baez RJ, Jones S, Lennon MA, Petersen PE, Rugg-Gunn AJ, et al. Fluoride and oral health. Community Dent Health. 2016;33(2):69–99.
123. Goldman AS, Yee R, Holmgren CJ, Benzian H. Global affordability of fluoride toothpaste. Glob Health. 2008;4:7.
124. Dickson-Swift V, Kenny A, Gussy M, de Silva AM, Farmer J, Bracksley-O'Grady S. Supervised toothbrushing programs in primary schools and early childhood settings: a scoping review. Community Dent Health. 2017;34(4):208–25.
125. Kranz AM, Duffy E, Dick AW, Sorbero M, Rozier RG, Stein BD. Impact of Medicaid policy on the oral health of publicly insured children. Matern Child Health J. 2019;23(1):100–8.
126. Watt RG, Rouxel PL. Dental caries, sugars and food policy. Arch Dis Child. 2012;97(9):769–72.
127. McKee M, Stuckler D. Revisiting the corporate and commercial determinants of health. Am J Public Health. 2018;108(9):1167–70.
128. Thow AM, Downs S, Jan S. A systematic review of the effectiveness of food taxes and subsidies to improve diets: understanding the recent evidence. Nutr Rev. 2014;72(9):551–65.
129. Nakhimovsky SS, Feigl AB, Avila C, O'Sullivan G, Macgregor-Skinner E, Spranca M. Taxes on sugar-sweetened beverages to reduce overweight and obesity in middle-income countries: a systematic review. PLoS One. 2016;11(9):e0163358.
130. Hyseni L, Atkinson M, Bromley H, Orton L, Lloyd-Williams F, McGill R, et al. The effects of policy actions to improve population dietary patterns and prevent diet-related non-communicable diseases: scoping review. Eur J Clin Nutr. 2017;71(6):694–711.
131. Schwendicke F, Thomson WM, Broadbent JM, Stolpe M. Effects of taxing sugar-sweetened beverages on caries and treatment costs. J Dent Res. 2016;95(12):1327–32.
132. Sowa PM, Keller E, Stormon N, Lalloo R, Ford PJ. The impact of a sugar-sweetened beverages tax on oral health and costs of dental care in Australia. Eur J Pub Health. 2018;29:173.
133. Briggs ADM, Mytton OT, Kehlbacher A, Tiffin R, Elhussein A, Rayner M, et al. Health impact assessment of the UK soft drinks industry levy: a comparative risk assessment modelling study. Lancet Public Health. 2017;2(1):e15–22.
134. Breda J, Jewell J, Keller A. The importance of the World Health Organization sugar guidelines for dental health and obesity prevention. Caries Res. 2018;53(2):149–52.

135. Beaglehole R, Bonita R, Horton R, Adams O, McKee M. Public health in the new era: improving health through collective action. Lancet. 2004;363(9426):2084–6.
136. Narvai PC, Frazão P. Práticas de saúde pública. In: Rocha AA, Cesar CLG, Ribeiro H, editors. Saúde pública: bases conceituais 2ª edição. São Paulo: Atheneu; 2008.
137. Benzian H, Hobdell M, Holmgren C, Yee R, Monse B, Barnard JT, et al. Political priority of global oral health: an analysis of reasons for international neglect. Int Dent J. 2011;61(3):124–30.

Water Fluoridation

Andrew John Spencer

Contents

29.1 Introduction – 438

29.2 Evolution of the Oral Epidemiological Evidence – 438

29.3 Findings from Across Clinical Trials to Monitoring Studies – 440

29.4 Understanding Heterogeneity and Bias in Studies of Water Fluoridation – 441

29.5 Study Design and Bias – 442

29.6 Exposure to Fluoride in Drinking Water – 443
29.6.1 Exposure: Induction Period – 443
29.6.2 Exposure to Naturally Occurring Fluoride in Early Research – 443
29.6.3 Exposure to Water Fluoridation: The First Community Trials – 444
29.6.4 Reviews of Community Fluoridation Trials – 444
29.6.5 Comparative Studies with Concurrent Controls: Continuous Residence or Lifetime Exposure to Fluoridated Water – 444
29.6.6 Lifetime Exposure to Fluoridated Water Among Adults and Older Adults – 445

29.7 Caries Outcomes – 446
29.7.1 Background – 446
29.7.2 Natural History and Intraoral Distribution of Caries – 447

29.8 Alternative Caries Outcome Measures – 448
29.8.1 A Different Approach: Incidence and Increment of Caries – 449

29.9 Conclusions – 449

References – 449

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_29

Learning Objectives

- Define water fluoridation.
- List the types of studies in their chronological sequence along the path to building the evidence on the effectiveness of water fluoridation.
- Compare the effect size of reduction in caries across studies by time and study design.
- What are the potential sources of bias in studies on water fluoridation?
- Differentiate the ways in which exposure has been measured in studies of water fluoridation.
- How can measurement of caries outcomes bias study findings?

29

29.1 Introduction

Oral epidemiology has played a central role in documenting the burden of oral disease, describing the natural history, establishing the risk of occurrence, investigating success in managing disease, and finally establishing paths for disease prevention. As dental caries is frequently described as the most common childhood noncommunicable disease and has the most substantial burden of illness among all oral diseases, it is not surprising that oral epidemiology has focused greatly on dental caries. Fortunately, oral epidemiology has contributed to the great progress in understanding the etiology and the opportunities for prevention of caries.

The use of fluorides, at a population level and individually, has been crucial to approaches to caries prevention. Fluorides have transformed oral health over the last 75 years. While fluoride does not vaccinate against caries, it has reduced the burden of caries by a staggering degree. What was once unmanageable by clinical restorative interventions has now become more manageable by the dental healthcare system in many countries. At the population-level fluoridation of drinking water, salt or milk has been the cornerstone for caries prevention. The widespread behavior of tooth brushing has also created an opportunity for caries prevention with fluoridated toothpaste. Together fluoridation and fluoridated toothpaste are credited with much of the decline in the burden of caries.

The evolution of fluoride as the central agent in caries prevention began with water fluoridation. Water fluoridation is the adjustment of the level of fluoride in a drinking water supply to achieve near maximal prevention of caries without the occurrence of dental fluorosis of public health or aesthetic concern. Water fluoridation has been acknowledged as one of the great public health measures of the twentieth century [1]. All formal reviews, whether systematic or narrative reviews, have concluded that water fluoridation is effective in reducing the prevalence and severity of dental caries in children and adolescents and increasingly young adults and adults.

29.2 Evolution of the Oral Epidemiological Evidence

The development of the theory and subsequently the evidence around the benefit of fluoridated drinking water followed a path of clinical cases, observation in a natural experiment, through to clinical trials, and then public health monitoring. In many respects this is a "classic" story within epidemiology. The following description of the evolution of the oral epidemiological evidence draws heavily on work by Whelton et al. [2]

From late in the nineteenth century, there was reference to the phenomenon of mottled enamel, enamel opacities which might take on staining and loss or pitting of the tooth enamel in its more severe form. McKay in 1916 [3] is credited with observing that children with mottled enamel, although their teeth seemed structurally imperfect, were less susceptible to dental caries. McKay [3] suspected that these outcomes were the result of something in drinking water but did not know what. The answer to what was in the drinking water, fluoride, came from Churchill in 1931 and was dependent on development of scientific instrumentation to measure low levels of fluoride in drinking water [4].

Initially the focus was on fluoride and mottled enamel. Dean and colleagues set about observing the prevalence and severity of mottled enamel across many communities in the USA. Dean developed a specific index, Dean's Index of Dental Fluorosis [5], and determined the dose-response relationship between naturally occurring fluoride in drinking water and the prevalence and distribution of dental fluorosis in communities. This observational research was conducted across some 22 communities [6, 7]. In the meantime, Ainsworth [8] had added to the reports that dental caries was lower in a community with a high fluoride level in drinking water. Interest grew in broadening the dose-response observational studies to consider both dental caries and dental fluorosis as outcomes. Bodecker and Bodecker [9] had developed measures for dental caries in individuals, and Dean and others applied these measures to early teenage children, 12–14 years old, in 21 communities mostly in Illinois and Texas in the USA [10, 11]. The "21 cities" study provided the dose-response evidence that generated the hypothesis that at around 1 mg F/L, there was near maximal prevention of dental caries without dental fluorosis of public health concern [12] (Fig. 29.1).

The benefit or harm of fluoride in drinking water was specified across populations with differing levels of naturally occurring fluoride in drinking water. The anal-

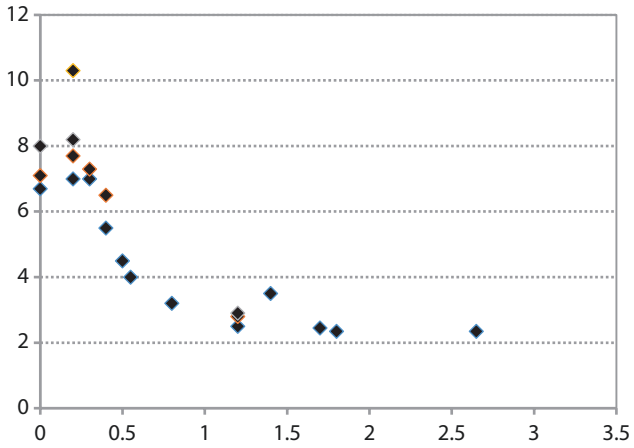


Fig. 29.1 Dose-response relationship between fluoride in a water supply and caries experience (DMFT) from Dean's 21 cities study [12]

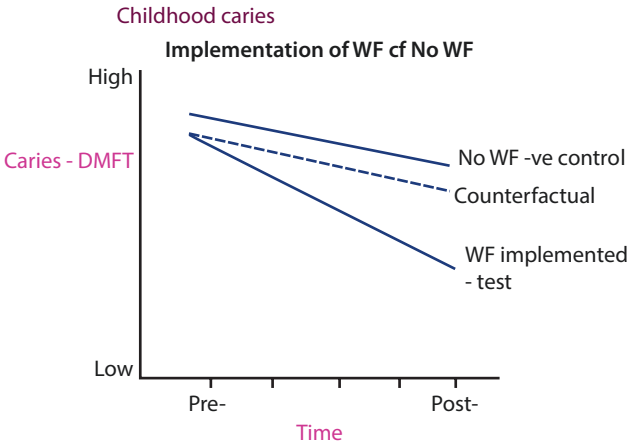


Fig. 29.2 Before and after non-randomized controlled study comparing non-fluoridated (No WF -ve control) to fluoridated (WF implemented- test) sites and the counterfactual

ysis focused on group differences not differences within a group [13]. It sought to find populations that had a low prevalence and experience of dental caries and a low prevalence of dental fluorosis.

A hypothesis emerged out of the dose-response data that the fluoride level in water supplies which had negligible fluoride could be adjusted upward to achieve a near maximal prevention of caries without endemic dental fluorosis of concern. This was articulated by Ast in 1943, and Dean in 1944 outlined the community fluoridation trials that would soon follow [12, 14]. Research entered a phase of foundational community fluoridation trials.

Community fluoridation trials were conducted as before and after non-randomized controlled studies. These are an attempt to mimic an experimental design using observational data, studying the differential effect of an intervention. They assess the effect of water fluoridation on caries in an intervention group by comparing the change over time in both the intervention and control groups. Such studies are prospective, comparing groups over time.

Some assumptions are involved in the comparisons usually stated as the counterfactuals: the preexisting or before differences are assumed to be fixed over time; and difference in the differences across time is assumed to be a causal effect (Fig. 29.2).

Three Trials were Commenced in the USA and One in Canada

- Grand Rapids (1945), Michigan, paired with nearby Muskegon and the naturally fluoridated Aurora, Illinois (1.2 mg F/L), as a positive control
- Newburgh (1945), New York, paired with Kingston, New York
- Evanston (1946), Illinois, paired with Oak Park, Illinois
- Brantford (1945), Ontario, paired with Sarnia, Ontario, and the naturally fluoridated Stratford, Ontario, as a positive control

The first findings from the Grand Rapids trial were released in 1950 [15]. These findings included the baseline and the 4-year follow-up data. This created a difficulty. The control site quickly became aware of the early findings of positive reductions in caries in the fluoridation site and sought to implement fluoridation. Muskegon fluoridated in mid-1951, eliminating the paired negative control. This contributed to the complexity of the way findings were reported for the Grand Rapids trial as it progressed. Many findings are presented as before and after comparisons in the trial site, something which becomes important in including/excluding this in evidence in later systematic reviews of the effectiveness of water fluoridation.

The findings in the USA and Canada spurred interest from other counties, and the research entered a replication phase. There are two aspects to the replication phase. First, the dose-response relationship between fluoride occurring naturally is a water supply, and caries experience was replicated in the USA and further countries in the late 1940s and through the 1950s [16]. The curvilinear relationship was confirmed and around 1.0 mg F/L was supported as the level at which near maximal reduction in caries experience was achieved in children. Second, water fluoridation was initiated in Australia, Belgium, Brazil, Canada, Chile, Colombia, El Salvador, Germany, Great Britain, Japan, Malaysia, the Netherlands, New Zealand, Panama, Sweden, and Venezuela [17]. Some countries initiated trials similar to the first wave of studies in the USA and Canada, notably the Tiel-Culemborg study in The Netherlands initiated in 1953 [18]; a study in Hastings, New Zealand,

initiated in 1954 [19]; and Watford, Kilmarnock, and part of Anglesey in the UK initiated in 1955–1956, with Sutton, Ayr, and the remaining part of Anglesey acting as control towns [20]. These further trials built up the body of evidence for the effectiveness of fluoridating drinking water for the prevention of caries in children and adolescents.

Over time fewer sites conducted trials. After all, the effectiveness of water fluoridation had been endorsed by the US Public Health Service in 1952, accepted by the WHO in 1958, and recommended with specific accommodation of varying climatic conditions by the US Health and Human Services in 1962. Further as population coverage by water fluoridation increased and then stabilized, there were fewer opportunities to conduct before and after non-randomized controlled studies. In theory other study designs could have been pursued that are at a similar level in the strength of evidence. These include cohort studies, case-control studies, and interrupted time series with a control group. These study types share a characteristic of attempting to establish time precedence of the exposure before the observation of the outcome in the intervention group in comparison to the control group. However, they have been rarely used in research around water fluoridation.

Attention turned to demonstration studies to establish the feasibility and applicability of water fluoridation in different environments, especially after the mid-1960s. Public health authorities desired information on whether water fluoridation was providing a benefit for their community of concern [21]. Two study designs were employed: ecological studies and cross-sectional concurrent controlled studies. In many circumstances these designs cannot establish the time precedence that exposure preceded the development of the disease outcome. However, Slade et al. [22] have pointed out that the temporal ordering between exposure and disease is still informed when studies compare lifetime exposure and non-exposure and when disease is quantified as lifetime, cumulative incidence, i.e., the DMFT measure in a study of dental caries. The ecological and cross-sectional studies vary in how the exposure is defined: ecological studies classify exposure of a group sharing an environment such as residence in a fluoridated area, whereas cross-sectional studies classify exposure at an individual level. While these observational study designs are regarded as lower in the evidence hierarchy, modern epidemiology and computing power has generated new analytic approaches that have added considerable confidence to the reduction of the risk of bias in these studies.

The path from clinical observation to a widely practiced public health measure of accepted benefit to the community has been long and involved studies of different design and quality. A notable feature is the consistency with which research along the pathway over 70 years has documented a benefit in prevention of caries associated with water fluoridation. Consistency across settings and study designs was identified as an important and useful criterion in evaluating and grading evidence in public health [23]. Together the evidence across this research has been sufficient for water fluoridation to be recognized as a great public health achievement.

29

29.3 Findings from Across Clinical Trials to Monitoring Studies

Early research on water fluoridation supported reductions of 45–60% in caries severity against control groups. In the Newburgh-Kingston trial, a consistent reduction in caries among children in the fluoridated town was found compared to the non-fluoridated town over an extended period. After 10 years the reductions in caries (DMFT) among 6–9-, 10–12-, and 13–14-year-old children ranged from 57 to 48%. The reduction in 16-year-old children was lower at 41% [24]. In the Evanston-Oak Park trial, caries in 12–14-year-old children in the fluoridated town decreased by 57% to 49% compared to the non-fluoridated town [25].

Two systematic reviews of the evidence from the before and after non-randomized controlled trials conducted in either the first wave of trials or the replication phase support the substantial difference in caries severity that emerged after the implementation of water fluoridation [26, 27]. Both systematic reviews ended up focused on dental caries in children. Both reviews included studies across a wide time span. For instance, Iheozor-Ejiofor et al. [27] review included studies from 1951 to 1984 and one more recent 2012 unpublished study.

The Iheozor-Ejiofor et al. [27] review included studies that reported on different ages of children and measures of caries. They estimated the pooled effect of water fluoridation on caries and examined the heterogeneity of the effect. The key findings are summarized in Table 29.1.

Iheozor-Ejiofor et al. [27] concluded that there were few recent studies meeting the review's inclusion criteria. Most of the available data came from studies conducted prior to 1975.This is consistent with the path that has been pursued in developing and then monitoring water fluoridation as a public health measure. There was a consistency in the direction of the findings across the studies, but there was heterogeneity in the size of the effect. This was evident across ages of children, caries measures, and time at which the study was conducted.

Table 29.1 Summary of the reductions in caries in children in before and after non-randomized controlled studies with different outcome measures from the systematic review by Iheozor-Ejiofor et al. [27] (2015)

Measure	No. of studies	Findings
2015 Iheozor-Ejiofor et al. review		**Before and after non-randomized controlled trials**
dmft	9	35% mean reduction with fluoridation 1.81 tooth reduction (95% CI 1.31–2.31)
DMFT	10	26% mean reduction with fluoridation 1.16 tooth reduction (95% CI 0.72–1.61)
% dmft = 0	10	15% mean increase with fluoridation (95% CI 11–19%)
% DMFT = 0	8	14% mean increase with fluoridation (95% CI 5–23%)

After NHMRC 2017 [28]

Estimates of the effect size for differences in caries in children also exist for studies out of the monitoring phase. The table below summarizes the findings of studies from a review of cross-sectional concurrent controlled studies [29]. Many studies were included. Table 29.2 presents the median reduction and the range from the individual studies. Table 29.2 also includes an individual study with a different study design, a multilevel ecological study [30]. The effect size of this multilevel ecological study was a 37–39% reduction in caries experience in fluoridated areas. The effect sizes of all the studies in Table 29.2 are not dissimilar to that observed for the before and after non-randomized controlled studies included in the Iheozor-Ejiofor et al. review [27].

One message from Table 29.1 and 2 is that the body of research on the effectiveness of water fluoridation consistently supports its benefit. This holds across different designs. However, the effect size in individual studies varies within studies of the same design and across studies of a different design. What is it in the methods of oral epidemiology applied to research on the effectiveness of water fluoridation that helps us understand this variation, and which should receive greater attention in future research so that estimates of effectiveness can more confidently inform public policy?

Table 29.2 Summary of the reductions in caries in children in studies of different designs (cross-sectional concurrent controlled and a multilevel ecological study) and with different outcome measures [28–30]

Measure	No. of studies	Findings
Rugg-Gunn and Do [29]		**Cross-sectional controlled studies**
dmft	19	44% median reduction with fluoridation (range 29–68%)
dft	2	47% median reduction with fluoridation (34–59%)
dmfs	7	33% median reduction with fluoridation (14–66%)
dfs	1	17% reduction with fluoridation
DMFT	37	37% median reduction with fluoridation (5–85%)
DMFS	12	29% median reduction with fluoridation (0–50%)
DFS	2	27% median reduction with fluoridation (10–44%)
Do and Spencer [30]		**Multilevel ecological study**
dmfs		39% mean reduction (95% CI 18–56%)
DMFS		37% mean reduction (95% CI 15–53%)

29.4 Understanding Heterogeneity and Bias in Studies of Water Fluoridation

It is clear from the evidence that emerged across the phases of the research on water fluoridation that a consistent finding is that water fluoridation is associated with a reduction in caries in children and adolescents. However there appears to be a reasonable level of heterogeneity in the actual effect size of the reduction of caries within studies of the same design and across study designs. Bias is a process at any stage of inference tending to produce results that depart systematically from true values [31].

True differences may exist between the findings of studies of the caries preventive effect of water fluoridation, particularly when studies are conducted in very different settings. Some heterogeneity may also be due to chance or random variation. Alternatively, differences may arise due to bias or systematic error. The risk

of bias has been related to study design. However, all studies of whatever design may be biased. So, while risk of bias may start with study design, other sources of bias need to be considered.

The following sections begin with consideration of study design as a risk of bias and consider several common sources of bias: confounding, contamination, and observer bias. In later sections, sources of bias associated with measurement of exposure and outcomes will be considered in greater depth.

29

29.5 Study Design and Bias

Study design is considered an indicator of risk of bias. The risk of bias associated with different study designs has been ordered into a hierarchy [32]. As water fluoridation is an intervention, the hierarchy for intervention studies is relevant. A systematic review of randomized controlled trials and at least one randomized controlled trial are at the peak of the hierarchy followed by a pseudorandomized controlled trial. No studies of water fluoridation fit these descriptions. Comparative studies with concurrent controls are at the next level. Numerous study designs fit this description. Nearly all studies of the effectiveness of water fluoridation are observational comparative studies with concurrent controls. This has led some to automatically brand the evidence on water fluoridation and caries as weak [33].

While study design is widely accepted as a primary criterion for assessing the susceptibility to risk of bias, there are criticisms. Even the acceptance that randomized controlled trials are of the greatest validity (or reduced risk of bias) has been criticized. Rothman [34] contends that it is a misconception that the comparative validity [or the reduction of the risk of bias] can be inferred from the type of study. It was argued by Rychetnik et al. [35] that study design is only one aspect of the assessment of quality (or risk of bias). There is a need to understand bias in studies in order to differentiate quality, particularly within a single level of evidence. Sources of bias include:

- Confounding
- Contamination
- Observer bias

Randomization is not feasible for a population intervention like water fluoridation. Therefore, there is a need to consider biases that arise from confounding due to differences between groups either at the initiation of a study or that emerge across time. The more similar the intervention and control groups, the less the risk of bias from confounders in comparative studies with concurrent controls. However, establishing how many or exactly what confounders need to be controlled varies considerably across studies. The consideration of confounders should be driven by conceptual models of the determinants of caries, each factor should be investigated for its relationship with the "exposure" and the "outcome," and appropriate analytic approaches should be pursued to adjust estimates of effect size.

Possible confounders in any comparative study with concurrent controls include sociodemographic/socioeconomic status: age and sex; parental/household social position (income, education, employment); and issues like rurality. Dietary pattern variation consumption of sweetened drinks may also be a confounder.

The abundant availability of other preventive services may vary across the intervention and control groups and lead to a "dilution" of the effect [36]. But if "dilution" is unequally distributed across intervention and control groups, it may create confounding. A special case of an unequal distribution of other preventive measures is co-intervention. Co-intervention occurs when members of the control group receive other effective interventions as a substitute for the intervention [37], in this case exposure to fluoridated water. Such a situation might involve a school-based fluoride rinsing program or application of fluoride varnish.

There are further factors that might bias studies around water fluoridation. Contamination is where the intervention is obtained in part or full by some in the control group. This is recognized as the "diffusion" of fluoride exposure into the control group via foods/fluids produced in a fluoridated area [36, 38]. Little progress is made on how to quantitatively measure and adjust for diffusion.

Observer bias may arise when the exposure status of either individuals or a group is known when outcomes are being assessed. Exposure means that a person has, before developing caries as a disease outcome, come into contact or ingested fluoride from drinking water [31]. In most studies of water fluoridation, the exposure status of groups is known to observers of the caries outcomes, and therefore observers may be biased.

Observer bias is reduced through blinding, but this has proved impractical in most research on water fluoridation. While blinding is theoretically important, there is no strong evidence that different findings exist between blinded and non-blinded studies of water fluoridation. Just one study has attempted blinding [39]. Its results were very similar to other studies of water fluoridation.

There is a movement toward greater consideration of the consequences of a lack of blindness. Sackett [37] argues that the consequence of a lack of observer blindness should be tested through reliability testing against a blind adjudicator. Fortunately, oral epidemiology places a strong emphasis on examiner reliability, including the use of a "gold" examiner, so this is an area that studies

on water fluoridation and caries should work to strengthen. It may also be argued that as many study participants may have mixed exposure histories, knowledge of current residence in a fluoridated or non-fluoridated area may not directly create an opportunity for observer bias.

Rychetnik et al. [35] considered that there needs to be an improvement in the understanding of bias and pragmatism about the importance of study design relative to other impacts on the risk of bias and assessment of quality. New study quality assessment tools place more emphasis on the quality of what was done. Sanderson et al. [40] identified a range of domains in tools to assess the level of evidence in observational studies. These included selecting participants, addressing design-specific sources of bias (recall bias, observer bias, loss to follow-up), methods for controlling confounding, analytic/statistical methods, and conflicts of interest, all of which are relevant to the susceptibility to risk of bias. Finally, a greater emphasis needs to be placed on measuring exposure and outcomes.

29.6 Exposure to Fluoride in Drinking Water

A further source of bias in studies and a source of heterogeneity in effect size across studies on water fluoridation relate to measurement of the exposure. Exposure means that an individual or group has, before the development of caries as the outcome, drunk fluoridated drinking water. As caries is a chronic, accumulating disease, that contact takes place over time. There are several ways of characterizing exposure to fluoridated drinking water. Choice of an appropriate exposure measure is made based on an understanding of the pathophysiology of caries and the biological mechanisms of the effect of fluoride on caries as a process.

29.6.1 Exposure: Induction Period

Early research around fluoride was focused on dental mottling, a developmental change in the tooth enamel characterized by opacities in its mild forms and breakdown of the integrity, pitting or flaking, of enamel in its more severe forms. The identification of fluoride occurring naturally in water supplies as the causative factor led to the term dental fluorosis. It is, therefore, not surprising that initially the action of fluoride in the prevention of caries was thought to be due to the incorporation of fluoride into the mineralizing hydroxyapatite crystals of enamel in the form of fluorapatite which was regarded as stronger. A greater understanding of cariology led to strength being replaced by resistance to demineralization. This can be described as a preeruptive mode of action.

The successful introduction of fluoridated toothpaste clearly indicated modes of action that operate after the mineralization of the tooth. Actions on the oral microflora and on the kinetics of demineralization and remineralization at the tooth surface became more prominent. These can be described as posteruptive modes of action.

The possible modes of action are important background to different induction periods of exposure to fluoride in drinking water and caries outcomes. Exposure to fluoride in drinking water during tooth mineralization is commensurate with a developmental "critical period" exposure. Exposure to fluoride after eruption of teeth and across a subsequent lifetime is commensurate with a "lifetime accumulation" exposure [41].

A narrative review by Beltran and Burt in the 1988 [42] examined clinical and observational research and concluded that 80 percent of the benefit of exposure to fluoride was posteruptive (topical) and 20 percent was preeruptive (systemic). Yet, the importance of different possible actions remains an area of contention. Observational research in the first community water fluoridation trials [24, 43], a replication study in the Netherlands [44], and hypothesis driven research in Australia [45]and Korea [46] all support a discernable role for preeruptive exposure in permanent dentition caries outcomes among children.

This highlights the need for care in considering both the timing of exposure and the length of time the exposure to water fluoridation lasts. The key underlying question is whether the exposure occurs across a relevant induction period [47]. Induction periods are usually defined for disease initiation, but here the induction period is one for disease prevention.

29.6.2 Exposure to Naturally Occurring Fluoride in Early Research

The earliest oral epidemiology on fluoride in drinking water and caries was conducted as dose-response research across populations with exposure to differing fluoride levels occurring naturally in water supplies. Exposure can be considered at a population level or at an individual level, sometimes a combination of the two levels.

Dean and colleagues characterized the differing exposures at a population level. However, Dean et al. also applied an element of an induction period by including only children "continuously exposed to the variable under investigation (the public water supply)," i.e., who had been in the community since birth and had

drunk the local tap water [11]. Dean was analyzing dose-response for caries among children with a lifetime of exposure to drinking water at various fluoride levels.

29.6.3 Exposure to Water Fluoridation: The First Community Trials

There are a great many publications that arose out of the first four community fluoridation trials over the 16–17 years of follow-up observed. Just as in the original dose-response research of Dean et al., child participants had to have resided in the city for the whole duration of the trial. For instance, Ast et al. [24] describe "This report [on the Kingston-Newburgh trial], however, is based only on those children who had been in continuous residence in Newburgh …, or who had been born there subsequent to that date and lived continuously in Newburgh to the time of the examination."

Further, findings of the trials noted that a child born before the implementation of water fluoridation could only have a fractional life exposure depending on their age at the time fluoridation commenced and the length of time over which follow-up occurred. Arnold [43] noted that in the Grand Rapids-Muskegon trial, water fluoridation effectively reduced caries in children who were continuously exposed to its effects from birth onward. However, Arnold also pointed out beneficial effects for those born prior to fluoridation. The size of the benefit in caries prevention observed was related to the proportion of life an age group had spent exposed to a fluoridated drinking water supply. Emphasis was given the developmental stage different teeth were at the time of the fluoridation of water supplies. This would be consistent with a critical period of exposure. The presence of a smaller preventive benefit among teeth which were developed prior to the implementation of water fluoridation would support a lifetime accumulation exposure hypothesis.

29.6.4 Reviews of Community Fluoridation Trials

Reviews like that of McDonagh et al. [26] (the York Review) and the more recent review by Iheozor-Ejiofor et al. [48] (the Cochrane Review) applied an inclusion criterion to the identified before and after non-randomized controlled studies that the follow-up period needed to be 3 years. The origin of the 3-year threshold is uncertain. It does match the traditional study period for randomized clinical trials of preventive agents, being particularly prominent in toothpaste trials for caries prevention. However, such a short period is at odds with the original dose-response research and fluoridation community trials.

Given the wide age range of children studied, from preschool children aged 4 years old to early teens aged 13–16 years old, the exposure to fluoridated drinking water may have been only a small proportion of a child's life at times of outcome assessment. The exposure may also sit uncomfortably as either a critical period exposure or a short accumulation exposure, or a bit of both.

It is clear from the McDonagh et al. review [26] but not from the Iheozor-Ejiofor et al. review [27] that years of exposure was considered a factor contributing to heterogeneity of the findings. The heterogeneity of the estimates of effectiveness associated with years of exposure calls for more attention to be paid to the exposure period. The inclusion of years of fluoridation as a covariate in regression analyses for heterogeneity in systematic reviews is but a starting point.

29.6.5 Comparative Studies with Concurrent Controls: Continuous Residence or Lifetime Exposure to Fluoridated Water

A common scenario of monitoring the effectiveness of water fluoridation post-1975 has been the cross-sectional concurrent controlled study. In general, this comparison has commented less on causality and more a confirmatory documentation that differences between those exposed and not exposed to water fluoridation still exist and are in the expected direction.

Unlike the before and after non-randomized controlled study, the counterfactual assumptions cannot be directly tested: first, that there is no difference between groups before exposure to fluoridated drinking water and, second, that the difference between the exposed and not exposed groups is due only to the exposure alone. Clearly these studies are at risk of bias, and some of these have been discussed earlier. However, in cross-sectional studies with concurrent controls, the issue of the measurement of exposure and the relevance of the induction period still exists.

A frequent application of the exposure measure in cross-sectional comparisons with concurrent controls has been the exclusion of children who have not had continuous residence in either the fluoridated or non-fluoridated area. In large national studies, this exclusion occurs at the stage of analyzing data. Research in the USA has nearly always been confined to children who are continuous residents at sites, combining an ecological approach with an individual exposure criterion [49]. A substantial proportion of children may not

be continuous residents of the sites, anything up to two-thirds of participants. This applied to Brunelle and Carlos's report on the 1986–1987 National Survey of US Schoolchildren and the difference in caries for continuous residents in fluoridated and non-fluoridated sites. A further example of this was the exclusion of more than half of the children in the 1986–1987 National Survey of US Schoolchildren in Heller et al.'s [50] analyses of a dose-response to fluoride levels in water supplies. This exclusion is a way of optimizing the estimate of effect size of water fluoridation. It is no longer documenting the effect of fluoridating a drinking water supply on a population which will always have a mix of exposure levels due to residential mobility, consumption of non-tap water, or use of effective drinking water filters. It is testing an association if all children comply with or adhere to the intervention protocol and have or not have an exposure across their lifetime to water fluoridation.

Some research has extended further into measures of individual exposure. This was proposed by Grembowski [51] when researching the impact of water fluoridation on the oral health and treatment costs of young adults in Washington state, USA. Grembowski proposed a measure of percent lifetime exposure to fluoridated water. The number of years people consumed fluoridated water in their lifetime was calculated from residential histories and national censuses on fluoridated water supplies (such censuses usually give the fluoride level and the year in which fluoridation was implemented). As fluoridation exposure is determined partly by age, Grembowski calculated the percentage of a person's lifetime exposed to fluoridated water. Lifetime fluoride exposure was found to be strongly associated with caries outcomes [52].

The same concept has been extensively used in research in Australia looking at water fluoridation and childhood caries outcomes. Slade et al. [53] used residential histories and documentation of the fluoride status of all communities over 200 people to map the percent lifetime exposure to fluoridated drinking water. Lifetime exposure to fluoridated water was found to be associated with caries outcomes, stronger for the primary dentition than the permanent dentition and in a state with lower population coverage by water fluoridation. This was explained by possible action of the diffusion effect, whereby the processed foods and fluids in a fluoridated area are transported into non-fluoridated areas introducing a "contamination" in the exposure pattern. The application of such individual measures of exposure changes subtly the research question. It is no longer a question of the effectiveness of a fluoridation program at a population level, but strength of association between exposure to fluoridated drinking water and caries outcomes. One advantage of this approach is that it creates a type of dose-response relationship. Further, by mapping the period of life with exposure to water fluoridation, the relative importance of the critical period or accumulation hypothesis can be tested as was done by Singh et al. in 2003 [45].

29.6.6 Lifetime Exposure to Fluoridated Water Among Adults and Older Adults

The measurement of exposure is even more important as the age group targeted in research increases. The issue of the effectiveness of water fluoridation in adults is a crucial issue in establishing the benefits of water fluoridation in a wider population than children and adolescents and to expressions of cost-benefit. Reviews like that of Griffin et al. [54] have estimated the effectiveness of water fluoridation in adults. They found that in five studies published after 1979, the preventive fraction was 27% (95% CI 19.4, 34.3%). Griffin et al. [54] stated that most adults in the included studies had lived all their life in the fluoridated or non-fluoridated area or the studies estimated the effect of exposure to fluoridated water controlling for potential confounding variables. However, it is not certain to what extent adults were excluded from analyses of the included studies under a lifetime residency inclusion criterion.

Do et al. [55] took a different approach in a recent primary study. They mapped out the exposure pattern of Australian adults (14+ years old) using a national oral health survey dataset complied in 2004–2006. All age groups had the potential of less than all their lifetime exposed to fluoridated water. However, the exposure profile of groups depended on their year of birth and the year at which water fluoridation was introduced in whatever cities they had had residence. The mean percent lifetime exposure and the interquartile range presented in ◘ Fig. 29.3 steadily decreased across older deciles of adults. If accumulation across a lifetime of the action of fluoride is important to the beneficial effect, then older adults can at best only show a partial effect. However, older adults are also unlikely to have an exposure in their early life given they may have been born prior to the implementation of fluoridation. If there is a critical period, then older adults will not have received this benefit.

The pattern of lifetime exposure to water fluoridation has a strong effect on the association of water fluoridation and adult caries. This is apparent in ◘ Table 29.3. Estimation of the effect size of water fluoridation in adults for the highest exposure quartile in younger age groups was significant, but the effect fell away in the 45+ age groups. A truncated distribution of percent lifetime exposure to water fluoridation contributes to this null finding.

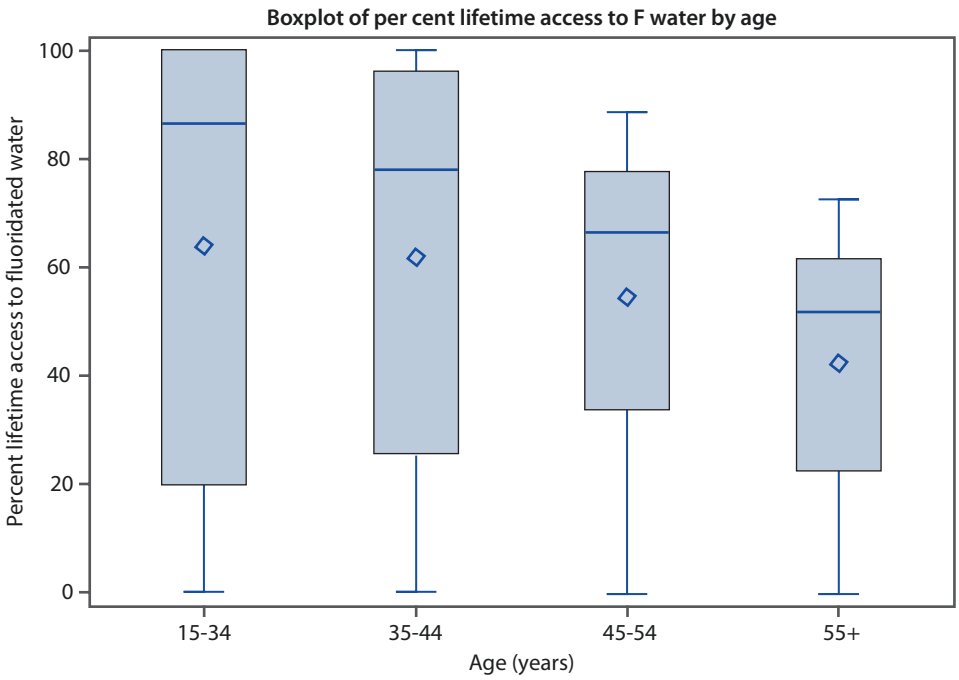


Fig. 29.3 Distribution of percentage lifetime exposure to water fluoridation by age groups in the Australian adults [55]. (Permission 19/03/19.) Rectangular box: interquartile range (IQR); small diamond: mean; horizontal line within the box, median; horizontal T lines, max and min values

Table 29.3 Adult caries outcome (DMFS) by percent lifetime exposure to water fluoridation (Do et al. 2017)

		Age		
% lifetime exposure to water fluoridation	15–34	35–44	45–54	55+
	Mean ratio			
Lowest quartile 0–20; 0- < 26; 0–34; 0–23	Ref	Ref	Ref	Ref
Highest quartile 100; 100; 78–89; 61–73	0.67 (0.48–0.92)	0.78 (0.66–0.93)	0.93 (0.82–1.04)	1.00 (0.93–1.08)

Water fluoridation is likely to be effective beyond the age of 35 years old. In addition to the issue of truncation of exposure, there is a likely saturation of the sites in the mouth which are likely to develop caries which obscures variation in the caries outcome measurement (See ► Sect. 29.7.2).

29.7 Caries Outcomes

29.7.1 Background

The caries process is continuously occurring in all individuals. However, in most individuals and at most sites in the mouth, the process ebbs and flows between demineralization and remineralization and basically is at an equilibrium. Occasionally, a local or a more generalized change in the oral environment will tip the process out of equilibrium, and demineralization will become dominant. If that continues for long enough, irreversible damage will occur to the enamel, and the underlying dentine of a tooth and a carious lesion will have formed. Such a lesion may go undiagnosed and extend. Alternatively, it may be diagnosed, and an intervention in the form of a filling could be placed. If the process is left undiagnosed or is not successfully treated for a long period of time, then deeper tissues within the tooth or at the apex of the root of the tooth may become involved, and a tooth may need complex treatment, or the tooth may be extracted.

Capturing observations of caries outcomes is a fundamental part of all oral epidemiology of caries. The methodology of oral epidemiological fieldwork is dominated by procedures for examiners to follow and criteria to be applied in making judgments about the presence

or absence of caries, now or in the past, at a tooth or tooth surface-level.

Most epidemiology focuses on the prevalence or incidence of a disease. Both are available as outcome measures for caries. However, more frequently oral epidemiological research is measuring prevalence and severity. In measuring severity oral epidemiology seeks to differentiate between individuals by the extent of caries experienced. This is done by calculating summary scores, the summed number of decayed, missing due to decay (extracted) or filled (due to decay) teeth (DMFT) or tooth surfaces (DMFS). When these measures refer to children's primary dentitions the nomenclature to use is lower case dmft/s, and when referring to the permanent dentition, the nomenclature to use is upper case (DMFT/S). Oral epidemiologists are so used to these measures that there is a risk that the different character of them and the relationship between them is not considered or explained. This can be a source of measurement bias. Understanding this risk depends on the underlying natural history and intraoral distribution of caries.

29.7.2 Natural History and Intraoral Distribution of Caries

The observable signs of caries and the summary measures for caries follow working rules. These are underpinned by a hierarchy of "zones" of caries attack first described by an Expert Working Group of the World Health Organization (WHO) as part of the International Dental Epidemiological Methods Series in 1967 [56]. Poulsen and Horowitz [57] examined this hierarchy against three separate studies data and offered some modifications, but the basic hierarchy was confirmed (Table 29.4).

Table 29.4 Hierarchy of teeth and tooth surfaces involved in the caries attack [56]

Zone	Description of teeth and surfaces involved
5	Proximal surfaces of mandibular anterior teeth (excluding distal surfaces of cuspids)
4	Labial surfaces of maxillary and mandibular incisors and cuspids
3	Proximal surfaces of maxillary anterior teeth (excluding distal surfaces of cuspids)
2	Proximal surfaces of posterior teeth (including distal surfaces of cuspids)
1	Pit and fissure surfaces of posterior teeth
0	None of the above

Bachelor and Sheiham [58] confirmed that the most susceptible tooth surfaces to decay are occlusal surfaces of first molars and buccal pits of lower first molars. If all the first molars have caries, then there is a high probability that the second molars will be affected. The occlusal surfaces of the second molars and the buccal surfaces of the second lower molars are the second most susceptible sites for caries. At higher DMFS, the mesial proximal surfaces on the upper molars are the next sites to be affected and then the lower proximal surfaces. These are followed by the occlusal surfaces of the first premolars and proximal surfaces of first molars and then the occlusal surfaces of second premolars and the proximal surfaces of second molars. These are followed by the occlusal surfaces of the second premolars and then the upper first premolars. At higher levels of caries, all surfaces of canines, smooth surfaces of premolars, and incisors are affected. Sheiham and Sabbah [59] extended the discussion of working rules on the natural history of caries. These working rules have relevance to understanding the heterogeneity in estimates of effect size and bias in the measurement of caries outcomes.

First, there is a defined relationship between caries prevalence and DMFT. This relationship was reported on by Knutson in 1958 [60] using data from the first series of fluoridation trials in the USA. Knutson defined the relationship with a catalytic equation $K\text{-}PREV = K^*(B)^{DMFT}$ where DMFT is the age-specific caries severity, PREV is the age-specific caries prevalence, and B and K are constraints for all age groups and populations. Others have tested the relationship with newer data and confirmed the working rule [61, 62]. The catalytic nature of the relationship captures a very rapid rise in prevalence against a slowly rising DMFT across modest DMFT scores, but then a plateauing of prevalence across higher DMFT scores. As the general relationship holds across age groups and populations, it assists in understanding the different estimates of effect size between prevalence and caries experience expressed as either dmft or DMFT (see Table 29.1 for the variation).

Second, there is a defined relationship between DMFT and DMFS. Again, this was first defined by Knutson [60]. However, understanding this relationship relies more on the hierarchy in the observed pattern of caries attack of teeth and tooth surfaces. As higher zone teeth and tooth surfaces become involved in the caries process, measures of caries experience will increase. This has been the basis of using observations on the involvement of zones to predict actual caries experience scores. However, a different aspect of this hierarchy of caries attack underlies the behavior of caries experience

outcome measures. Progression to higher zones also involves a general movement from posterior to anterior teeth and pit and fissure to proximal to free smooth surfaces being involved in the caries attack. Thus, pit and fissure surfaces of posterior teeth are the first teeth and surfaces and the proximal surfaces of the same posterior teeth are the next surfaces to show evidence of the caries attack. Progressing from Zone 1 to 2 may not involve a change in DMFT score, but DMFS will be higher for those who have reached Zone 2 in the caries attack process. A similar disconnect occurs for free smooth surfaces and proximal surfaces of various anterior teeth. Both DMFT and DMFS will be higher as one progresses to higher zones, but the rate of increase will not be linear or equal.

Water fluoridation is known to prevent caries in a preferential manner from free smooth surfaces to proximal surfaces to pit and fissure surfaces [63]. A consequence of this is that free smooth surfaces of anterior teeth are more likely to be saved from caries ahead of proximal surfaces of anterior teeth, and proximal surfaces of posterior teeth are likely to be saved from caries ahead of pits and fissures of those same teeth. A working rule of caries is that as caries in populations is successfully prevented, caries in the least susceptible surfaces (free smooth and proximal surfaces) decreases considerably more than in the most susceptible surfaces (pits and fissures) [64].

The pattern of teeth and tooth surfaces affected by caries and the preferential benefit of water fluoridation across different surfaces explain two issues in the evidence on effect size for caries prevention by water fluoridation. These are:

- The variation across measures for prevalence and caries experience and within caries prevalence at the tooth and surface level
- The finding that higher baseline caries experience is associated with larger effect size

The size of the percentage reduction in caries outcomes appears greater in situations where there is more caries activity and when caries outcomes are measured at the tooth surface level than tooth level than at the level of prevalence. Similar consideration underlies the differences observed in the effect of water fluoridation in the primary and permanent dentitions.

Brunelle and Carlos [65] reported on the 1986–1987 US National Survey of Schoolchildren. They reported a greater percentage reduction in caries at the surface level in the primary dentition of 5-year-olds (39%) than in the 12-year-olds (17%) [49].

29.8 Alternative Caries Outcome Measures

A feature of caries experience measures is that each of the possible presentations, an untreated carious tooth, a missing tooth, and a filled tooth, contributes equally to the summed tooth-level score. Yet, these presentations may represent quite different extent of disease on an individual tooth. A similar situation exists for the summed score at the tooth surface level, although there are attempts to adjust for the number of surfaces a missing tooth might contribute to the summed score.

There have been proposals to weight the components in a way that reflects the number of functioning teeth or sound tooth substance present. Sheiham et al. [66] proposed the functioning teeth and T-Health indices. The functioning teeth index is an aggregate of the number of filled (otherwise sound) teeth and sound teeth, each being of equal value. This presupposes that sound and restored teeth have, all other things equal, equivalent function and benefits. The T-Health index represents the amount of sound tooth tissue. A sound tooth will contain more sound tooth tissue than a filled tooth, while the latter was proposed to have more sound tissue than a decayed tooth. Later, filled and decayed teeth were considered to have the same amount of sound tooth substance [67]. Missing teeth have no sound tissue.

Jakobsen and Hunt [68] used data from three national oral health surveys in the USA and a state level survey in Iowa to show that functioning teeth and T-Health indices were more capable of detecting changes in oral health than the traditional DMF index. Birch [69] used a similar approach to the T-Health measure to simulate the effect of water fluoridation on oral health. Birch assigned values to the presentation of each tooth – sound, filled, filled and decayed, and decayed and missing – and used the sum as a "quality-adjusted tooth stock." Others like Fyffe and Kay [70] have explored more complex utility functions. Lewis [71] examined weighted indices and utility functions from the DMF index. Lewis concluded that a utility-weighted version of the DMF index has more theoretical validity, but that it does not necessarily lead to more sensitive outcome measure of caries.

The dominance of the traditional caries prevalence and experience measurement in the oral epidemiology around water fluoridation is somewhat unfortunate. Such measures are not readily interpretable by the public. Some effort has gone into other self-reported measures that have more ready interpretation. Self-reported measures of oral health such as a global rating of oral health or a version of oral health-related quality of life might be more reflective of community valuations of oral health outcomes [72].

29.8.1 A Different Approach: Incidence and Increment of Caries

Some of the concerns with the risk of bias with exposure measurement and measurement of outcome might be reduced if rather different study designs were more commonly pursued in research about the effectiveness of water fluoridation. Cohort studies which follow exposure and the incidence or increment of caries across time offer advantages in studies among adults. Exposure can be determined across a relevant time, possibly as short as that adopted for clinical trials. Outcome can be measured by tracking the change in tooth surface status. This may circumnavigate the problems of exposure for only a fraction of a full lifetime and the recurrence of caries at teeth or tooth surfaces that have already experienced caries and therefore show no increment in the summed scores for caries experience. This is especially relevant in middle and older-aged adults where the caries experience may approach saturation.

One such study was conducted by Hunt et al. [73] in Iowa among an older adult population, 65 years old or more. The incidence of caries was compared among those long-term residents in a fluoridated and non-fluoridated community. Exposure was therefore a combination of an ecological measure with an element of individual exposure history as an inclusion criterion. Exposure was measured over a 30-year period, implying a need for a long lead time for accumulation of fluoride's action. The incidence of caries across an 18-month period was lower in those adults who had resided in a fluoridated community for more than 30 years. Hunt et al. concluded that water fluoridation appeared beneficial even though exposure to fluoridated water began in adulthood and therefore fitted a posteruptive exposure and accumulation hypothesis.

This study provides an indication of evidence that can be obtained in a relatively short time period. Refinement of the way exposure is measured at an individual level might see such an approach have greater applicability especially among adults.

29.9 Conclusions

A benefit of water fluoridation in the prevention of caries is a consistent finding in all the stages of development and implementation of water fluoridation as a public health measure. These include dose-response studies, community fluoridation trials, and monitoring of the outcomes of fluoridation programs. However, there is a good deal of heterogeneity in the effect size across individual studies. This heterogeneity reflects different study designs and the risk of bias. Confounding, contamination, and observer bias are frequently considered as sources of bias. Two additional sources of potential bias are examined: measurement of exposure and outcome. There are many ways in which measurement of exposure and outcome can contribute to study findings not reflecting a true result, that is, being biased. Hopefully consideration of these measurement issues will lead to greater attention being paid to them in the interpretation of the results of existing studies or in future studies of water fluoridation.

References

1. (US) CDC. Ten great public health achievements – United States, 1900–1999. Morb Mort Weekly Rep (MMWR). 1999;48:241–3.
2. Whelton HP, Spencer AJ, Do LG, Rugg-Gunn AJ. Fluoride revolution and dental caries: evolution of policies for global use. J Dent Res. 2019;98:837. (Accepted 16 March 2019).
3. McKay FS, Black GV. An investigation of mottled teeth: an endemic developmental imperfection of the enamel of the teeth, heretofore unknown in the literature of dentistry. Part 1. Dental Cosmos. 1916;58:477–84.
4. Churchill HV. Occurrence of fluoride in some waters of the United States. J Dent Res. 1932;12:141–8.
5. Dean HT. Classification of mottled enamel diagnosis. J Am Dent Assoc. 1934;21:1421–6.
6. Dean HT, Elvove E. Some epidemiological aspects of chronic endemic fluorosis. Am J Pub Health. 1936;26:567–75.
7. Dean HT, Elvove E. Further studies on the minimal threshold of chronic endemic fluorosis. Pub Health Rep. 1937;52:1249–64.
8. Ainsworth NJ. Mottled enamel. Br Dent J. 1933;55:233–50, 274–76
9. Bödecker CF, Bödecker HWC. Practical index of varying susceptibility to dental caries in man. Dental Cosmos. 1931;73:707–16.
10. Dean HT, Jay P, Arnold FA Jr, Elvove E. Domestic water and dental caries. II. A study of 2,832 white children, aged 12–14 years, of 8 suburban Chicago communities, including Lactobacillus acidophilus studies of 1,761 children. Pub Health Rep. 1941;56:761–92.
11. Dean HT, Arnold FA Jr, Elvove E. Domestic water and dental caries. V. Additional studies of the relation of fluoride domestic waters to dental caries experience in 4,425 white children, aged 12 to 14 years, of 13 cities in 4 states. Public Health Rep. 1942;57:1155–79.
12. Dean HT. Post-war implications of fluorine and dental health: epidemiological aspects. Am J Pub Health. 1944;34:133–43.
13. Rose G. Sick individuals and sick populations. Int J Epidemiol. 2001;30:427–32.
14. Ast DB. The caries-fluorine hypothesis and a suggested study to test its application. Pub Health Rep. 1943;58:857–77.
15. Dean HT, Arnold FA, Jay P, Knutson JW. Studies on mass control of dental caries through fluoridation of the public water supply. Pub Health Rep. 1950;65:1403–8.
16. Murray JJ. Prevention of oral disease. 3rd ed. Oxford: Oxford University Press; 1992.
17. World Health Organization (WHO), Expert Committee on Water Fluoridation. First report of the Expert Committee on Water Fluoridation. Geneva: WHO; 1958.

18. Kwant G, Houwink B, Backer Dirks O, Groeneveld A, Pot T. Artificial fluoridation of drinking water in the Netherlands; results of the Tiel-Culemborg experiment after 16 1/2 years. Netherl Dent J. 1973;80(Suppl 9):6–27.
19. Ludwig TG. Hastings fluoridation project V1–dental effects between 1954 and 1970. N Z Dent J. 1971;67:155–60.
20. DHHS. The fluoridation studies in the United Kingdom and the results achieved after eleven years; a report of the committee on research into fluoridation. DHSS Reports on Public Health and Medical Subjects No. 122. London: Department of Health and Social Security; 1969.
21. Public Health England. Water fluoridation: health monitoring report England. London: Public Health England; 2018. p. 2018.
22. Slade GD, Grider WB, Maas WR, Sanders AE. Water fluoridation and dental caries in U.S. children and adolescents. J Dent Res. 2018;97:1122–8.
23. Harder T, Abu Sin M, Bosch-Capblanch X, Coignard B, de Carvalho GH, Duclos P, et al. Towards a framework for evaluating evidence in public health. Health Policy. 2015;119:732–6.
24. Ast DB, Smith DJ, Wachs B, Cantwell KT. Newburgh-Kingston caries-fluorine study. XIV. Combined clinical and roetgenographical dental findings after 10 years of fluoride experience. J Am Dent Assoc. 1956;52:314–25.
25. Blanney JR, Hill IN. Fluorine and dental caries. J Am Dent Assoc. 1967;74:233–302.
26. McDonagh M, Whiting P, Bradley M, Cooper J, Sutton A, Chestnutt I. A systematic review of water fluoridation (York review), NHS Centre for Reviews and Dissemination, University of York. York: York Publishing Services Ltd; 2000.
27. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM. Water fluoridation for the prevention of dental caries. Cochrane Database Syst Rev. 2015;(6):CD010856.
28. National Health and Medical Research Council (NHMRC). Information paper – Water fluoridation: dental and other human health outcomes, report prepared by the Clinical Trials Centre at University of Sydney, Canberra: NHMRC, 2017. Accessed: www.nhmrc.gov.au/guidelines/EH43.
29. Rugg-Gunn AJ, Do L. Effectiveness of water fluoridation in caries prevention. Community Dent Oral Epidemiol. 2012;40:55–64.
30. Do GL, Spencer AJ. Contemporary multilevel analysis of the effectiveness of water fluoridation in Australia. Aust NZ J Pub Health. 2015;39:44–50.
31. Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. 2nd ed. Baltimore: Williams and Wilkins; 1988.
32. National Health and Medical Research Council (NHMRC). NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, Commonwealth of Australia; 2009.
33. Wilson PM, Sheldon TA. Muddy waters: evidence-based policy making, uncertainty and the 'York review' on water fluoridation. Evid Policy. 2006;2:321–31.
34. Rothman KJ. Six persistent misconceptions. J Gen Intern Med. 2014;29:1060–4.
35. Rychetnik L, Fromer M, Hawe P, Shiell A. Criteria for evaluating evidence on public health interventions. J Epidemiol Community Health. 2002;56:119–27.
36. Ripa L. A half-century of community water fluoridation in the United States: review and commentary. J Public Health Dent. 1993;53:17–44.
37. Sackett DL. Commentary: Measuring the success of blinding in RCTs: don't, must, can't or needn't? Int J Epidemiol. 2007;36:664–5.
38. Griffin SO, Gooch BF, Lockwood SA, Tomar SL. Quantifying the diffused benefit from water fluoridation in the United States. Community Dent Oral Epidemiol. 2001;29:120–9.
39. Thomas FD, Kassab JY. Fluoridation in anglesey: a clinical study of dental caries in mothers at term. Br Dent J. 1992;173:136–40.
40. Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 2007;36:666–76.
41. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285–93.
42. Beltran ED, Burt BA. The pre- and post-eruptive effects of fluoride in the caries decline. J Public Health Dent. 1988;48:233–40.
43. Arnold FA Jr. Grand rapids fluoridation study – results pertaining to the 11th year of fluoridation. Am J Pub Health. 1957;47:539–45.
44. Groeneveld A, van Eck AAMJ, Backer DO. Fluoride in caries prevention: is the effect pre- or post-eruptive? J Dent Res. 1990;69(Special Issue):751–5.
45. Singh KA, Spencer AJ, Armfield JM. Relative effects of pre- and post-eruption water fluoride on caries experience of permanent first molars. J Public Health Dent. 2003;63:11–9.
46. Cho H-J, Lee H-S, Paik D-I, Bae K-H. Systemic effect of water fluoridation on dental caries prevalence. Community Dent Oral Epidemiol. 2014;42:341–8.
47. Rothman KJ. Modern epidemiology. Boston: Little, Brown and Co; 1986.
48. Iheozor-Ejiofor Z, O'Malley LA, Glenny AM, Macey R, Alam R, Tugwell P, Walsh T, Welch V, Worthington HV (2013). Water fluoridation for the prevention of dental caries (Protocol). Cochrane Database Syst Rev. 2013(12):CD010856.
49. Newbrun E. Effectiveness of water fluoridation. J Pub Health Dent. 1989;49 Spec Issue:279–89.
50. Heller KE, Eklund SA, Burt BA. Dental caries and dental fluorosis at varying water fluoride concentrations. J Pub Health Dent. 2007;57:136–43.
51. Grembowski D. Measuring length of exposure to fluoridated water. Community Dent Oral Epidemiol. 1988;16:131–4.
52. Grembowski D, Fiset L, Spadafora A. How fluoridation affects adult dental caries. J Am Dent Assoc. 1992;123:49–54.
53. Slade GD, Davies MJ, Spencer AJ, Stewart JF. Associations between exposure to fluoridated drinking water and dental caries experience among children in two Australian states. J Pub Health Dent. 1995;55:218–28.
54. Griffin SO, Regnier E, Griffin PM, Huntley V. Effectiveness of fluoride in preventing caries in adults. J Dent Res. 2007;86:410–5.
55. Do L, Ha D, Peres M, Skinner J, Brun R, Spencer AJ. Effectiveness of water fluoridation in the prevention of dental caries across adult age groups. Community Dent Oral Epidemiol. 2017;45:225–32.
56. World Health Organization (WHO). International dental epiodemiological methods series. Manual no. 3. (First draft). Geneva: WHO; 1967.
57. Poulsen S, Horowitz HS. An evaluation of the hierarchical method of describing the pattern of dental caries attack. Community Dent Oral Epidemiol. 1974;2:7–11.
58. Bachelor PA, Sheiham A. Grouping of tooth surfaces by susceptibility to caries: a study in 5-16 year-old children. BMC Oral Health. 2004;4:2.
59. Sheiham A, Sabbah W. Using universal patterns of caries for planning and evaluating dental care. Caries Res. 2010;44:141–50.
60. Knutson JW. Epidemiological trend patterns of dental caries prevalence data. J Am Dent Assoc. 1958;57:821–9.
61. Lilienthal B, Andrews NH. The applicability of Knutson's index of prevalence of dental caries to data for Australian, Formosan and Indonesian children. Arch Oral Biol. 1961;3:207–16.

62. Spencer AJ, Lewis J. The relationships between prevalence of caries, percentage with active caries and caries severity. Aust Dent J. 1987;32:441–5.
63. Backer DO. The benefits of water fluoridation. Caries Res. 1974;8(Suppl 1):2–15.
64. McDonald SP, Sheiham A. The distribution of caries on different tooth surfaces at varying levels of caries-a compilation of data from 18 previous studies. Community Dent Health. 1992;9:39–48.
65. Brunelle JA, Carlos JP. Recent trends in dental caries in US children and the effect of water fluoridation. J Dent Res. 1990;69(Spec Issue):723–7.
66. Sheiham A, Maizels JE, Cushing AM. New composite indicators of dental health. Community Dent Health. 1987;4: 407–14.
67. Marcenes WS, Sheiham A. Composite indicators of oral health: functioning teeth and the number of sound equivalent teeth (T-health). Community Dent Oral Epidemiol. 1993;21:374–8.
68. Jakobsen JR, Hunt RJ. Validation of oral status indicators. Community Dent Health. 1990;7:279–84.
69. Birch S. Measuring dental health: improvements on the DMF index. Community Dent Health. 1986;3:303–11.
70. Fyffe HE, Kay EJ. Assessment of dental health state utilities. Community Dent Oral Epidemiol. 1992;20:269–73.
71. Lewis JM. Improving dental health status indicators for evaluation. Community Dent Oral Epidemiol. 1996;24:32–6.
72. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health. 1994;11:3–11.
73. Hunt RJ, Eldredge JB, Beck JD. Effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population. J Pub Health Dent. 1989;49:138–41.

Teaching Oral Epidemiology

Richard D. Holmes and Georgios Tsakos

Contents

30.1 Introduction – 454

30.2 Regulation of the Teaching Curriculum – 454

30.3 Course Documentation and Design – 454
30.3.1 Course or Study Guide – 454
30.3.2 Learning Objectives – 455
30.3.3 Methods of Teaching and Learning – 456

30.4 Curriculum Content – 458

30.5 Assessment Methods – 459

30.6 Quality Assurance Methods – 461

30.7 Conclusions – 461

References – 461

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_30

Learning Objectives

- To provide students with important basic knowledge in relation to the main principles and concepts of epidemiology
- To facilitate a thorough understanding of the different epidemiological study designs and link it with key knowledge in relation to the epidemiology of oral conditions
- To identify and incorporate learning objectives and outcomes published by relevant dental professional/regulatory bodies into curriculum design, teaching content and assessments of epidemiology for oral conditions
- To list some of the common methods for the delivery and assessment of teaching alongside their advantages and disadvantages from the perspectives of learners and teachers
- To be aware of blended approaches to teaching and assessment that may facilitate learning and engage students as active rather than passive learners
- To appreciate the need for robust quality assurance methods to ensure high-quality teaching and assessments based upon multiple sources of evidence and feedback

30

30.1 Introduction

For dental students and dental professionals undertaking formal undergraduate (pre-doctoral) courses of study, the subject of oral epidemiology may initially appear as a highly specialised area for postgraduate study and research potentially remote from the practise of clinical dentistry. Although the dental undergraduate curriculum will vary between institutions and across countries, it is often subjects such as the biosciences, human anatomy, behavioural science and communication skills that predominate at early stages in training. Moreover, clinical training is more associated with passive learning and focused primarily on acquiring technical expertise and mastering the necessary details for clinical success. On the other hand, oral epidemiology focuses upon the analysis and interpretation of data at the population rather than the individual level and is by nature based on adopting a more critical approach and the scientific paradigm based on logical deduction and scientific reasoning. This can present challenges for academics attempting to integrate and promote the subject within the student body – especially at an undergraduate level. Epidemiology is concerned with the distribution and determinants of disease and injury within populations and it seeks to ask the questions: 'what is happening?', 'where is it happening?' and 'to whom?', thereby focusing on the distribution of the diseases and their determinants in the population and promoting critical thinking, a central requirement in modern day curricula. It is the role of teachers in this discipline to instil with students at an early stage in their development, the importance and relevance of oral epidemiological principles to the practise of clinical dentistry. Being the most relevant discipline to healthcare decision-making [1], the teaching of epidemiology should have a critical and central role in the whole curriculum.

30.2 Regulation of the Teaching Curriculum

Higher education institutions (HEI) prepare undergraduates for their first professional registration in dentistry, and they are often subject to formal regulation and/or accreditation by an external body. These regulatory organisations typically oversee and monitor the training and education of dental professionals at national levels. Whilst each HEI will have its own process for developing curricula and for quality assuring its educational programmes, it would be wise for teachers to familiarise themselves with the published competencies or subject domains expected of the national regulator in relation to oral epidemiology. Table 30.1 provides selected examples of these expectations which are relevant to oral epidemiology and set at the level of a newly qualified general dentist. The three countries selected include Australia, USA and the United Kingdom. The examples listed in Table 30.1 provide elements of a useful framework to guide undergraduate teachers in their development of course curricula for oral epidemiology. The selected examples in Table 30.1 represent high-level indicators of the relevant dental regulators' (or dental education association's) expectations in relation to subjects which may include epidemiology. From these areas or curriculum domains, it is possible to map a wider course curriculum, devising specific learning objectives, outcomes, lesson plans and ultimately, assessments.

30.3 Course Documentation and Design

30.3.1 Course or Study Guide

It is strongly recommended that a written course or study guide is provided to inform students of the key elements of teaching and assessment associated with the course. A suggested example for the core content of this document is shown (Table 30.2); however, each educational institution may have its own approved template. Indeed, this should not be seen as an extensive list, and it is recommended that a further breakdown of learning objectives and core reading by each session (or groups of sessions) may further facilitate clarity over

Table 30.1 Selected expectations of national regulators and dental educational organisations linked to oral epidemiology for newly qualified dentists across three countries

Country	Regulatory body or educational organisation	Selected expectation/s on graduation associated with oral epidemiology teaching	Category
Australia	Australian Dental Council [2]	Critical Thinking – Locate and evaluate evidence in a critical and scientific manner to support oral health care	Competency
		Scientific and Clinical Knowledge – Understand the theories and principles of population oral health	Competency
USA	American Dental Education Association [3]	Critical Thinking – Evaluate and integrate emerging trends in health care as appropriate	Competency
		Utilise critical thinking and problem-solving skills	Competency
United Kingdom	General Dental Council [4]	Explain the principles of oral epidemiology and critically evaluate their application to patient management	Learning Outcome
		Critically appraise approaches to dental research and integrate with patient care	Learning Outcomes

Table 30.2 Core content of course or study guide

Section	Content
Introduction	Welcome message from Course Lead to course participants
Aims/ Objectives/ Outcomes	Expectations – list may be grouped by knowledge, skills and attitudinal domains or competencies
Learning & Teaching	Course structure, grouped by theme/ topics/modules with names of course leads and their contact details. Gantt chart outlining key dates in the course
Learning Resources	Core or recommended textbooks, links to online learning resources (VLE), expectations re. self-directed learning (private study)
Assessment	Grading and performance criteria. Assessment methods and contribution (weighting) within the wider course or qualification. Potential outcomes/awards for excellence

expectations and promote more in-depth learning within the overall framework of the course. Consideration should be given to the method for dissemination. Some students may prefer a hard (paper) copy, whilst others will prefer an electronic format for use with tablets or laptop computers. One benefit of using a virtual learning environment (VLE) is that this information remains available online for the duration of the course as a repository for students and the learning resources (e.g. presentation slides, web links, worksheets and assessment information) can be added and updated as the course progresses.

30.3.2 Learning Objectives

Both learning objectives and learning outcomes are terms that are frequently used interchangeably in course documentation; however, they are not the same. Within a course of study, learning objectives provide a statement of intent outlining what students can expect in terms of the development of their knowledge and skills. Conversely, learning outcomes focus more upon describing a measure of achievement expected on completion of the course of study. Whilst students may not tend to study learning objectives/outcomes in-depth, they can prove helpful when structuring modules or themes within a wider course of study. Ultimately, learning objectives/outcomes may help students to identify the extent of their perceived knowledge and understanding in preparation for assessments and examinations. For this reason, it is recommended that learning objectives/outcomes are clearly detailed within formal course documentation as an explicit aide-memoire for students, teachers and to inform relevant stakeholders (e.g. external examiners), who may be involved in quality assurance.

In writing a new learning outcome for a course of study, it can be helpful to consider their construct. A learning outcome may comprise three core elements:

- What the student will be able to do
- In what context
- How well they will do it

For example, a detailed learning objective may state: 'At the end of the oral epidemiology course, students will be able to: Explain trends in the distribution of dental disease using population-level data to support the findings of the final assessed literature review in Year 2'. Whilst the following learning objective may use less meaningful language and is therefore of limited value to students: 'By graduation, students will know how to use statistics in epidemiology and be aware of the statistical tests available'.

A widely used classification for ordering learning objectives and outcomes is Bloom's taxonomy [5]. Bloom divides these outcomes into three categories: affective, cognitive and psychomotor. One of the reasons why Bloom's taxonomy has become so popular within educational environments may relate to the intuitive nature of the model which can act as a user-friendly framework in which to nest the design of a new course or the development of existing teaching and assessment methods. Figure 30.1 illustrates the ordered learning goals ranging from 'remember' (e.g. simple recall of basic facts about epidemiological principles), through to 'application' (e.g. ability to apply the correct statistical test to a specific problem), all the way up the taxonomy to 'create' (e.g. the ability to produce new/original work through hypothesising, planning and design).

It is important to acknowledge that Bloom proposed his model as a hierarchical taxonomy and each layer is aggregated and incorporated into the higher level. For example, a new pre-doctoral student beginning their first exposure to the principles of oral epidemiology may start with assimilating core facts about research study designs and biostatistics. However, a postgraduate student may be required to synthesise data from previous studies whilst leading original research for a dissertation or thesis (analogous to the 'create' level) and is acknowledged to have mastered the lower levels of the model. For example, a learning objective for a postgraduate-level student that relates to oral epidemiology could be in terms of the student's ability to distinguish between confounding and effect modification or in terms of applying the criteria for causality in epidemiology to the association between a risk factor and an oral disease (e.g. sugars and caries).

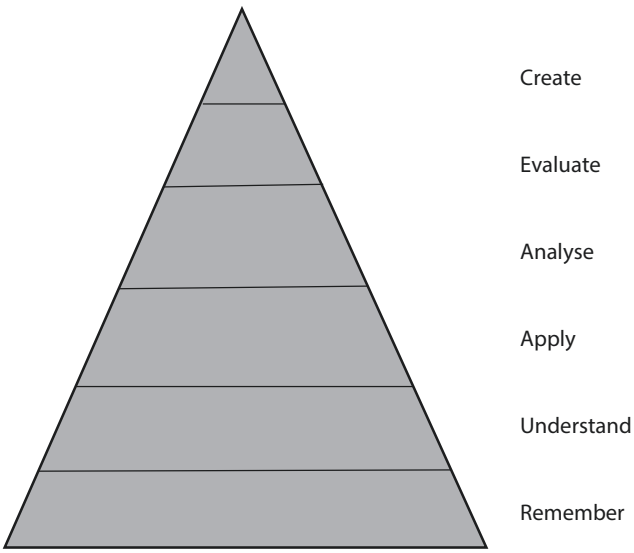


Fig. 30.1 Bloom's taxonomy [5]

30.3.3 Methods of Teaching and Learning

A thorough understanding of population demography, health trends and their context in healthcare systems and health policy is vitally important for dentists graduating to practise as team members [6]. Within the discipline of oral epidemiology, individual subjects may be taught using different approaches. For example, teaching the fundamentals of biostatistics or research study designs may initially adopt a 'teacher-centred' approach focused upon traditional lectures or class-based activities to impart the key facts. However, to teach both these subjects in full in such a formal environment with little input or engagement by students may prove challenging for students and their teachers. Consequently, students often prefer more varied and active approaches to learning [7]. Such 'student-centred' approaches may involve a range of methods from lecture-based teaching sessions to practical activities perhaps involving the familiarisation, analysis and interpretation of statistical data [8]. Data may be drawn from real national and international oral epidemiological surveys to maximise their relevance and applicability. Different questions or challenges may be posed for small groups to answer before the subject is 'pulled together' by the teacher with learning drawn from the wider student body. A combined approach could also be very helpful, whereby an initial lecture is followed up by a practical session whereby students are challenged (individually or in groups) with the help of a larger number of practical tutors in applying the knowledge conveyed in the lecture to promote in-depth understanding of key epidemiological features reported in studies from the literature. This helps bring the theoretical underpinnings of epidemiology into a practical application and makes the whole subject more relevant while also promoting critical thinking.

As an academic subject, oral epidemiology lends itself well to complementary or blended teaching meth-

ods including e-based learning (e.g. the familiarisation and use of statistical packages online), problem-based learning and tailored 1:1 tutorials for those who may require detailed feedback or support. Tailored support may perhaps be of most relevance to postgraduate research students or pre-doctoral candidates undertaking a unique thesis or dissertation. Table 30.3 lists some common teaching approaches together with their

Table 30.3 Common teaching approaches with selected advantages and disadvantages

Teaching method	Brief description	Selected advantages (+) and disadvantages (–)
Lecture	A more traditional, formal, larger-group teaching style. Students are largely passive recipients of facts, principles and theory	+ Efficient use of limited contact teaching time (if student group is large) + Useful if the student body is being introduced and/or has limited experience in the subject area – Students largely inactive, which may hinder interest/learning – Lecture duration may be long, comprising students' abilities to concentrate
Seminar/group teaching	More informal, smaller group of students (compared to lecture) led by a teacher or guest speaker. Typically involves engagement between students/teacher through active discussion. Could be done as a practical with a more experienced tutor leading it and more tutors helping and probing students in smaller groups to address the problems posed	+ Stimulates students to engage with the subject matter, peers and teacher + May enhance students' motivation for learning about the subject – Timetabling multiple small group teaching sessions may prove challenging for the available resources – Risk of inconsistency in the delivery of teaching between sessions which may affect student experience/evaluation
1:1 tutorial	Personalised teaching, discussion and feedback between student and teacher.	+ Relatively intensive, tailored support to facilitate enhanced learning and understanding + Active engagement in discussion, enhancing relevance and value to the student – Costly in time needed for the teacher and in timetabling sessions for multiple students – For the teacher, this may require knowledge of student performance/specific issue prior to the meeting requiring preparation time
Problem-based learning (PBL)	Group work where a problem or scenario requires student teams to manage the issue and identify the knowledge/skills to arrive at potential solutions	+ A student-centred approach that can improve communication and interpersonal skills which are transferable + Permits the use of multiple resources which may facilitate students who prefer different learning styles – Some students may feel unprepared or lacking in basic information to perform the task – The learning experience may be compromised for some if roles and contributions vary significantly within the group
e-learning	Online resources, e.g. a Virtual Learning Environment (VLE), providing study material in various formats including videos, audio recordings, website links, research papers and perhaps a course-specific discussion board. A specific example may be the 'flipped classroom'	+ The materials are available to students anywhere, at any time using a secure log-in and internet connection + Can prove an efficient use of time for teachers and students – Risk of demotivation with students who prefer face-to-face contact. There is a risk of isolation for some students if the course is delivered fully online – A degree of self-motivation required by the learner to actively engage with the learning material
Independent study (including research thesis)		+ Permits increased coverage of the learning material and study of areas of particular interest in greater depth + Reduces the emphasis upon classroom teaching delivered at a specific time and date, led predominantly by the teacher – Student must take responsibility for their time management and commitment to their learning alongside competing interests – Less-confident students may lack the readily available guidance and encouragement typical of a classroom environment

selected advantages and disadvantages. The list is not exhaustive and other teaching approaches exist together with further examples that may be subsumed within the categories listed (e.g. 'the flipped classroom', enquiry-based learning and critical reflection). Clearly, the chosen teaching approach is likely to depend upon the actual subject under study and size of the cohort involved. Consequently, it can be helpful to 'frame' the teaching of epidemiology around the educational level of students, recognising that there may be differences in the learning needs and goals of pre-doctoral students compared to those undertaking more advanced study [9]. Case-Study 1 box details a small-group teaching exercise used over several years with pre-doctoral dental students studying together via teleconferencing between the UK and USA.

Tip (Case-Study 1)

The Newcastle-Indiana dental education initiative brings together small groups of pre-doctoral dental students from Newcastle University (UK) and Indiana University (USA) to learn about dental health policy and the oral health of local communities in both countries. Prior to an annual exchange visit, live webinars are used to develop students' communication skills and awareness of population oral health in both countries. One exercise involves discussion of an open-access oral epidemiological research paper [10]. The paper acts to prompt discussion about the oral health of each nation, as well as acting as a tool to identify potential methodological considerations and limitations when comparing national oral epidemiological surveys.

Resource: Guarnizo-Herreño et al. *(2015)* [10]

Tip

Journal club to support the teaching of oral epidemiology.

Alongside the teaching of research study designs pertinent to oral epidemiology, the addition of an inter-related Journal Club may allow students to develop their critical analytic, communication and reflection skills – either individually or in small groups, depending upon the size of the class. Carefully chosen research papers will provide valuable opportunities to discuss the appropriateness of the epidemiological study design and statistical tests used by the authors and will act as a focus for discussion linked to interpretation of the quantitative data presented, implications and the conclusions drawn.

Tip

Integration of oral epidemiology into the wider curriculum.

Particularly at the pre-doctoral level, students may benefit from signposting about the role and impact of oral epidemiology across a range of (clinical) dental disciplines. For this reason, it is important that oral epidemiology is not taught in isolation as an academic subject, but as an 'applied' science. Study documentation should contain clear links to other courses being studied at the same time (emphasising the potential for horizontal integration), as well as highlighting how students' knowledge and skills in this discipline may be developed over time and across the academic years (vertical integration). Lastly, it can be helpful if teachers of other clinical and academic disciplines make explicit links to epidemiological principles in their own course documentation and teaching.

30.4 Curriculum Content

The taught content and subject matter within a course of study will be driven by factors including the level of educational award (pre-doctoral or post-doctoral), the length of the course of study and whether the course is standalone, or a single unit within a larger qualification or degree programme (e.g. DDS/BDS). Despite these variables there are many core epidemiological principles, concepts and skills that are common to the study of oral epidemiology. At the undergraduate level, basic statistics are usually integrated in the oral epidemiology course or module, thereby making the necessary links between the relevant epidemiological methods to address a research question with the appropriate statistical analysis and interpretation of findings. At a postgraduate level, the emphasis shifts towards a more in-depth conceptual and advanced methodological understanding, therefore statistics and oral epidemiology tend to become distinct but still highly interlinked modules in the curriculum.

Differences and variation may therefore be reflected in the wording of the course aims and learning objectives. For example, a short oral epidemiology course for qualified dentists may state in its learning objectives: 'participants will have *gained awareness* and *increased confidence* in applying a framework to guide the critical appraisal of research papers', whilst the same learning outcome for a postgraduate student specialising in this subject area may state that students would be expected to '*master the analytical and interpretive skills* required to critically

appraise study designs, statistical findings, methodological limitations and the implications of the research on oral and general health'. Consequently, knowledge and understanding of the principles and applications of epidemiology are central to the critical appraisal of literature and the overarching approach of evidence-based practice that should underpin the whole curriculum.

Table 30.4 lists some of the core areas for oral epidemiology teaching at the undergraduate level, together with suggestions for the level of attainment expected. For postgraduate and doctoral research candidates, a more advanced level of attainment would be expected, and it can be surmised that a large number of curriculum areas listed in Table 30.4 would move from simply 'defining' and 'being aware' of the topic in question to students being able to analyse, evaluate and apply principles with greater mastery of the subject matter. While the emphasis is clearly on oral health, it is common practice for the students to also be exposed to key areas from medical epidemiology.

Table 30.4 Core areas for oral epidemiology teaching at an undergraduate (pre-doctoral) level

Core subject area (with *selected* examples)	**Anticipated learning level**
Describing disease within populations Prevalence Incidence Standardised data	Awareness and interpretation
Measures of disease frequency and conditions Indices and their construct/ideal properties dmft/DMFT (decayed missing and filled teeth) CPI (Community Periodontal Index) IOTN (Index of Orthodontic Treatment Need), etc.	Awareness, application and interpretation
Describe and critically evaluate basic study designs Cross-sectional, case–control, cohort, randomised-controlled trials Systematic reviews and meta-analysis of primary data	Awareness and interpretation
Sampling strategies	Awareness and explain
Bias and confounding (including methods to control these risks in the design of studies and in the analysis of data)	Awareness, explain and interpret
Validity and reliability of research methods and data	Awareness and explain
Association and causation	Awareness, explain and interpret
Basic statistical tests including statistical significance, confidence intervals, advantages and disadvantages of these tests and thresholds	Awareness, explain and interpret
Multivariable analysis – linear and logistic regression	Awareness and interpret
Ethical issues in the design and conduct of oral/dental health surveys	Awareness
National/international epidemiological oral/dental health surveys Methodologies Trends in dental caries, periodontal disease, oral cancer and other common conditions Epidemiology relevant to and applied across the life course	Awareness, interpret and explain
Implications of dental and oral epidemiological findings for populations, dental professionals, healthcare services, health policy and other relevant stakeholders	Awareness and interpret
Synthesise the key findings from dental and oral epidemiology research papers	Awareness, interpret and explain

30.5 Assessment Methods

A wide range of assessment methods are available to measure students' knowledge and understanding of oral epidemiology. Different assessment methods may be selected to assess specific skills or knowledge, and Table 30.5 lists some of the options and their selected advantages and disadvantages. The list is not exhaustive and as with the selection of teaching methods, it is often beneficial to consider a blend of assessment methods than relying upon a single approach.

Assessments may be divided into two broad categories: 'formative' and 'summative'. Formative assessment is generally used for providing feedback and in the monitoring of students' performance within a course of study, perhaps at numerous time points. This type of assessment can yield useful information for learners with respect to their strengths and weaknesses and can be considered helpful in monitoring progress and identifying ongoing learning needs. In essence, formative assessment is part of on-going learning and it is the feedback session that fol-

Table 30.5 Common assessment methods with selected advantages and disadvantages

Assessment method	Brief description	Selected advantages (+) and disadvantages (−)
Single Best Answer (SBA)	A question (stem) is followed by a number of options, only one of which is the best (correct) answer. A variant of the SBA format includes the more traditional Multiple Choice Questions (MCQs)	+ A relatively efficient method for assessing a wide subject area using a large number of questions + Candidates' answers may be scanned using optical mark sheets, requiring little examiner input −More likely to focus upon simple factual recall rather than higher level skills (but not in every case) − May encourage guessing by candidates who do not understand the subject matter, but who guess correctly
Short answer	Various formats exist. Questions may range from the succinct: 'Write short notes on 'x' to a longer question with multiple sub-sections, leading candidates through a theme, scenario or concept. In each case the candidate writes their responses directly on to the examination paper or into an examination booklet.	+ Students provide the answers which may reduce guessing (unlike SBA-style questions where incorrect answers are suggested) + Question format is appropriate for and commonly used in both formative and summative assessments − May assess superficial knowledge only, with little focus upon higher level thinking or analysis − Handwritten responses require the involvement of an examiner
Essay	Long discursive writing in response to a set question or scenario. Candidates' work typically includes full sentences, paragraphs and may incorporate evidence and argument	+ Great potential to cover the widest range of learning objectives including high-level critical thinking and reasoning + Develops students' abilities to present a balanced/unbiased argument whilst potentially improving communication and presentation skills − Significant time is required to mark scripts which may prove difficult for large classes and small teaching teams − Examiner comments and grades can appear subjective without tight marking criteria, raising questions about examiner reliability
Clinical	Multiple formats exist including OSCE (Objective Structured Clinical Examination) and MOSLER (Multiple Objective Structured Long Examination Record)	+ Structured marking scheme for improved examiner consistency + Generates data for formative feedback on individual candidates and the course as a whole − Heavily resource intensive from the perspective of examiners, significant prior organisation and staffing − Oral epidemiology may receive little weighting in comparison to mainstream clinical subjects
Dissertation/Thesis	A significant and extended piece of academic writing, based upon original research or review/secondary analysis of existing data. Typically used towards the end of pre-doctoral programmes. May be supplemented by a viva (oral) examination	+ Allows students to show extensive breadth and depth in their understanding/knowledge of complex issues, principles, theories and arguments + May assist students to develop an interest in research/academia and improve their written/oral communication and analytical skills − Assessment is a very time-consuming process May require a second examiner for moderation purposes − Structure and presentation issues may overshadow content unless there are clear grade categories for content and presentation known to candidates in advance

lows the formative assessment that primarily promotes understanding through more in-depth discussion and explanation of the key areas assessed. Conversely, summative assessment usually quantifies attainment of knowledge and/or skills against the published course or degree learning outcomes. It is summative assessment that students typically associate with 'high stakes' examinations. This form of assessment may additionally adopt a more longitudinal and cumulative perspective to knowledge, perhaps assessing a whole academic year or degree programme. Whichever approach is taken, the course documentation should clearly outline which elements of the course are subject to formative and/or summative assessment and when they are scheduled to take place.

When designing assessments, it is critical that consideration is given to their validity and reliability alongside a number of important and related issues [11]. Standard setting should be used to determine what is the 'acceptable level' (i.e. the pass mark) for each assessment. The pass mark may be supplemented with additional thresholds (e.g. for meritorious performance or borderline failure), according to local regulations and for student feedback.

30.6 Quality Assurance Methods

Robust processes should be in place to ensure the provision and delivery of high-quality education for students attending a course of study. For education providers, quality assurance responsibilities typically involve explicit consideration of the setting and maintaining of academic standards; the provision of accessible and accurate information; the extent to which the course of study prepares students to achieve the course/degree published outcomes and finally, how teaching approaches may be developed and enhanced in response to student, examiner, institutional and, where necessary, national regulator feedback (which may be associated with professional accreditation).

Table 30.6 lists the types of quality assurance (QA) methods available. The chosen methods should be detailed in the course documentation so that they are available to students and interested stakeholders (e.g. external examiners and professional regulators). The methods for quality assurance should explain when and how each are applied within the course of study and where the findings will be considered (e.g. a Board of Studies or Quality Assurance Committee) for action to be taken if it is deemed necessary.

Table 30.6 Selected quality assurance methods and areas for evaluation

QA methods	Area of focus
Student-Staff Committees	Feedback
Course/module/programme questionnaires (online or paper-based)	Feedback
Internal and External Examiners	Feedback, calibration and external QA perspectives
Regulator/Accreditation Inspection	External feedback and benchmarking for professional registration
Regular and ongoing staff development opportunities and appraisal	Peer review and training
Periodic review of Strengths, Weaknesses, Opportunities & Threats (SWOT analysis)	Local policies and procedures
Formal written course documentation	Local policies and procedures
Fitness to study/practise, academic misconduct, appeals and student progression pathways	Local policies and procedures
Methods of teaching and assessment including grading criteria and matrices for classifying achievement outcomes	Local policies and procedures
Institutional oversight, staffing ratios, teaching support, innovation and investment	Institutional/provider standards

30.7 Conclusions

This chapter has provided a brief framework for key elements associated with the teaching of oral epidemiology across different educational levels. Following consideration of any national dental regulatory requirements or educational expectations, the curriculum, teaching and assessments may be adapted to fit alongside specific course learning objectives or outcomes. Students often prefer blended or active approaches to learning, and this chapter has provided examples of methods for teaching and assessment alongside some of their selected advantages and disadvantages. Additionally, an overview of core subject areas associated with the teaching of oral epidemiology has been suggested. The depth of teaching in these areas may be interpreted flexibly, depending upon the educational level of learners. Continuously improving teaching, learning and assessment through multi-source feedback will facilitate course improvements if they are needed. Considering and acting upon these issues will contribute to students' positive experiences of their teaching in oral epidemiology and maximise their potential to succeed.

References

1. Muir Gray JA. Evidence-based healthcare. Edinburgh: Churchill Livingstone; 1997.
2. Australian Dental Council. Professional competencies of the newly qualified dentist. February 2016. Online at: https://www.adc.org.au/sites/default/files/Media_Libraries/PDF/Accreditation/Professional%20Competencies%20of%20the%20Newly%20Qualified%20Dentist_rebrand.pdf

3. American Dental Education Association. ADEA competencies for the new general dentist. J Dent Educ. 2015;79(7):813–6.
4. General Dental Council. Preparing for practice – Dental team learning outcomes for registration (Revised edition). 2015. Online at file:///H:/Downloads/Preparing%20for%20Practice%20(revised%202015)%20(2).pdf.
5. Bloom BS. Taxonomy of educational objectives: the classification of educational goals. New York: Longmans, Green; 1956.
6. Gallagher J, Field JC. The graduating European dentist—domain IV: dentistry in society. Eur J Dent Educ. 2017;21(Suppl.1):25–7.
7. Goldmann E, Stark JH, Kapadia F, McQueen MB. Teaching epidemiology at the undergraduate level: considerations and approaches. Am J Epidemiol. 2018;187(6):1143–8.
8. Rubio M, Sánchez-Ronco M, Mohedano R, Hernando A. The impact of participatory teaching methods on medical students' perception of their abilities and knowledge of epidemiology and statistics. PLoS One. 2018;13(8):e0202769.
9. D'Agostino EM, Hlaing WM, Stark JH. Teaching on the continuum: epidemiology education from high school through graduate school. Am J Epidemiol. 2019;188(6):979–86.
10. Guarnizo-Herreño CC, Tsakos G, Sheiham A, Marmot MG, Kawachi I, Watt RG. Austin powers bites back: a cross sectional comparison of US and English national oral health surveys. BMJ. 2015;351:h6543.
11. Patel US, Tonni I, Gadbury-Amyot C, Van der Vleuten CPM, Escudier M. Shaping the future of dental education: assessment in a global context: an international perspective on dental education. Eur J Dent Educ. 2018;22(Suppl. 1):21–7.

Further Reading

Daly B, Batchelor P, Treasure ET, Watt RG. Essential dental public health. 2nd ed. Oxford: Oxford University Press; 2013.
Pine CM, Harris RV. Community oral health. 2nd ed. London: Quintessence; 2007.
Tsakos G, Baelum V. Chapter 23 - Dental epidemiology. In: Olsen J, Greene N, Saracci R, Trichopoulos D, editors. Teaching epidemiology: a guide for teachers in epidemiology, public health and clinical medicine. 4th ed. Oxford: Oxford University Press; 2015. p. 429–43.

Methods

Contents

Chapter 31 Measurement Instruments for Use in Oral Epidemiology – 465
João Luiz Bastos, Michael E. Reichenheim, and Claudia L. Moraes

Chapter 32 Reproducibility and Validity of Diagnostic Tests – 479
Renato Pereira da Silva, Andréa Videira Assaf, and Antonio Carlos Pereira

Chapter 33 Quantitative Bias Analysis in Dental Research
Quantitative Bias Analysis in Dental Research – 495
Murthy N. Mittinty

Chapter 34 Reviews Systematic and Meta-analysis – 507
Roger Keller Celeste and Falk Schwendicke

Measurement Instruments for Use in Oral Epidemiology

João Luiz Bastos, Michael E. Reichenheim, and Claudia L. Moraes

Contents

31.1 Introduction – 466

31.2 Epidemiology as a Measuring Exercise – 466

31.3 Points to Consider When Selecting Measurement Instruments – 467

31.3.1 What to Do When Instruments Are Available and Ready to Use (Scenario 1) – 470

31.3.2 Recommendations When Instruments Are Available, but Their Use in the Given Sociocultural Context Requires Additional Work (Scenario 2) – 472

31.3.3 Procedures When No Instruments Are Available or Those That Exist Are Insufficient, Requiring the Development of New Ones for the Underlying Research to Be Conducted (Scenario 3) – 474

31.4 Conclusions – 476

References – 476

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_31

Learning Objectives

- Familiarize the reader with concepts and principles for measuring constructs in oral epidemiology.
- Discuss the basic steps to be constructs when measuring oral health constructs within acceptable levels of validity, reliability, and comparability.
- Provide guidance on practical issues involved in the immediate use, cross-cultural adaptation, or development of new measurement instruments in oral epidemiology.

31.1 Introduction

One of the most important decisions to make in any epidemiological study in the field of oral health is to define which strategies to use in the data collection process. Part of this involves clearly specifying the source and procedures to accrue quality data. For example, will data be obtained from large databases available in health information systems? Will face-to-face interviews be conducted, or will self-completed forms be used, be it on paper or online? Besides, will other characteristics be assessed, such as oral health conditions, weight, height, and the consumption of certain foods? Once a general plan has been decided upon, it is important to select the questionnaires (hereafter, referred to as measurement instruments or measurement tools) to be utilized for data collection, thorough choices needing to be made in light of prior evidence on their validity and reliability. Studies providing information on the "general performance" of the instruments are thus required [1]. An instrument's validity is defined by the extent to which the measurements seize the "true" values of the construct under scrutiny. Assuming its validity, differences between the computed scores can be taken to reflect real differences between study participants or any other units of analysis. The reliability of an instrument, in turn, is more closely related to measurement reproducibility, whether data is obtained by different observers in one sitting or conducted by the same observer (or even self-administered by the same respondent) at successive points in time.

If the aim is, for instance, to conduct a study on determinants of dental caries, the quality of the measurements on food consumption, access to and use of oral health services, and exposure to fluoride sources are essential. Researchers must ensure that all these constructs or variables are assessed with high standards of quality. Validity or reliability flaws may hamper or even hinder the achievement of the research objectives: to produce trustworthy estimates concerning the frequency, distribution, and determinants of dental caries [2].

Although validity and reliability are widely discussed in the context of oral epidemiology, there is little debate about these concepts in scientific books or articles, especially in relation to measurement tools. It is not uncommon to find publications with extensive appraisals of theories, methods, and techniques commonly employed in oral epidemiology, but with just a few lines geared towards the development or cross-cultural adaptation of measurement instruments. Similarly, scientific articles frequently provide detailed description on sampling processes, data collection, and statistical techniques, but set aside little space to outline and debate the quality and scope of the measurement instruments employed.

This chapter aims to provide a detailed account on basic concepts and principles in the development or cross-cultural adaptation of measurement instruments in oral epidemiology. The topics are presented critically in the context of oral epidemiology, ranging from the development of multi-thematic questionnaires to the comparison of quantitative results across studies. The relation between epidemiology and measurements is presented first, followed by an appraisal of principles guiding the selection of measurement tools to be used in an investigation. Next, we provide three research scenarios and how the researcher may proceed accordingly; when (1) measurement instruments are available and ready to use; (2) tools are available, but their use requires additional work; and (3) no instruments are available or those available are inadequate, calling for the development of new instruments. In closing we offer some final thoughts on the subject.

The present chapter is admittedly introductory. Extensive accounts on the topics addressed here may be found in the cited references, as well as the final section containing additional reading suggestions.

31.2 Epidemiology as a Measuring Exercise

There is ample literature on how epidemiology may be defined [3]. In this chapter, we take epidemiology as having three fundamental goals: to study (1) the frequency, (2) the distribution, and (3) the determinants of health conditions in a given population. Highlighting these three goals presumes a specific set of phenomena/characteristics to be assessed in a particular sociocultural context. Studying, for example, the frequency of periodontal diseases in a given population draws upon key features, such as gingival bleeding, accumulation of dental calculus, probing depth, and alveolar bone loss, all of those involving measurement strategies that are specific to an oral examination per se.

The same applies to the other two elements defining epidemiology. To study the distribution of periodontal diseases according to age, for instance, age should be assumed to exist, and strategies should be devised to measure it. Investigating what the causes of periodontal diseases are implies assuming that these are real. Epidemiologic research is thus based on the measure-

ment of health conditions and the relations they may establish with other factors or characteristics. To undertake epidemiologic research in the field of oral health is, in other words, to engage in the continuous measurement and analysis of relations within a specified sociocultural context.

Although some oral health conditions and their causes may be directly assessed, others are less evident, demanding specific assessment strategies to be quantified [4]. The association between dental caries and oral health-related quality of life (OHRQoL) is a case in point. Whereas dental caries is often measured with the use of dental probes and dental mirrors, the approach to measuring OHRQoL is rather different. The latter cannot be directly assessed and can only be established by referring to a subset of its more tangible manifestations [4–6], including difficulty eating or limited ability to speak due to problems with the teeth, mouth, or dentures.

Although the use of techniques and resources to measure conditions that are more concrete occupies a central role in oral health studies, measurement of less tangible phenomena is similarly crucial. This is not only the case of OHRQoL, but also dental anxiety, orofacial pain, satisfaction with dental services, and the like. These are all constructs requiring measurement instruments comprised of items that, in tandem, allow their manifestation and intensity to be tapped.

What is then needed to measure something that is not directly observable? The first move is to have a clear conceptual definition as to what is meant to be measured [4–6]. Taking OHRQoL as an example, one definition widely held in the literature is "the absence of negative impacts of oral conditions on social life and a positive sense of dentofacial self-confidence" [7]. Note that the concept of *negative impact* is at the core of OHRQoL. Clearly, negative impact cannot be observed directly. Negative impact is manifested by an array of symptoms, such as those referred to by scholars in the field: (i) speech limitations; (ii) eating difficulties; (iii) shame as a result of the teeth, mouth, or dentures; (iv) difficulty relaxing; and (v) feeling of pain in the mouth.

> Assessing OHRQoL is thus not based on measuring negative impact per se, but the physical, cognitive, or emotional consequences that this state implies. This means that measuring it has to do with identifying its different ways of expression [4–6, 8].

In a clinical context, these manifestations are generally gauged through a careful appraisal of the patient's history in the form of interviews. The health professional and the patient may make use of some kind of standardized instrument to achieve this goal [9]. This instrument may be presented in a variety of forms, usually comprising items or assertions on the most common manifestations of the construct under scrutiny. For instance, an instrument devised to assess OHRQoL might have the following three items: "Have you experienced any difficulty eating because of your teeth, mouth, or dentures?", "Do you find it difficult to relax because of your teeth, mouth or dentures?", and "On a day-to-day basis, do you feel any pain relating to your teeth, mouth or dentures?" These items refer to three of many possible forms by which negative impact may manifest itself. Furthermore, these items clearly refer to distinct levels of negative impact.

This is how measurement instruments are usually developed and proposed. They make use of items reflecting low, moderate, or high intensities of an underlying construct.

> The responses to a set of items enable placing individuals under investigation within a spectrum of intensity [4] – ranging from a presumed absence to a very high level of impact of the features under scrutiny (teeth, mouth, or dentures) on quality of life.

This positioning of an individual on a gradient does not differ much from what may be obtained when measuring directly observable phenomena, such as dental caries or periodontal diseases. Evaluating study participants as to the presence and extent of tooth decay requires ranking them according to the impact the disease exerts.

In a clinical setting, patients and health professionals may opt not to use standardized measurement instruments to determine the presence and extent of a particular condition. In oral health studies, however, use of measurement instruments is often mandatory due to larger sample sizes.

31.3 Points to Consider When Selecting Measurement Instruments

> When deciding which instruments to use in a given study, it is important to select not only those enabling valid and reliable assessments of the relevant constructs, but also those that allow comparisons across similar studies, carried out in distinct sociocultural contexts.

Establishing comparability of results derived from multiple investigations is paramount to ascertaining the consistency of research findings [10, 11]. To be able to reproduce findings addressing the same research questions is pivotal in building up scientific knowledge. Although a single study may show that the implementation of a specific oral health policy has an expressive

impact on OHRQoL, only the accumulation of research corroborating or refuting this relationship may lend credence to such finding. When a series of quantitative studies is performed, however, the idea of consistency is only achieved when the results of these studies are comparable with each other.

The solution to this predicament involves using valid (thus equivalent) and reliable measurement instruments. By equivalent we mean measurement instruments assessing the same construct and allowing some quantitative comparison across results [12–14]. Stating, for instance, that the frequency of low OHRQoL in Brazil differs from Australia is impossible simply because their frequencies are 30% and 15% in each country. To be able to compare these results, we need to examine whether the construct has been similarly defined in both studies and whether it was measured using equivalent tools. Assessing quality of life with an item on "difficulty concentrating on everyday activities, like work or study, because of the teeth, mouth or dentures" does not necessarily generate results that are comparable to those derived from an item on "whether the teeth, mouth or dentures have negatively affected the respondent's speaking capacity." These two items not only refer to different levels of intensity in terms of negative impact but are also limited in the extent to which they reflect a continuum of intensity. Two individuals endorsing these items in separate studies would not be directly comparable.

Hence, the selection of measurement instruments plays a key role in oral epidemiology. Good practice suggests that any decision should be informed by a set of theoretical perspectives, including those held by cross-cultural psychology researchers [12]. Scholars from this field of knowledge assume that any given sociocultural context encompasses a system of beliefs and values with important linguistic, behavioral, and moral specificities. The expression of abstract constructs may thus entail distinctive definitions and interpretations in certain sociocultural milieus, which may directly affect quantitative comparisons if not attended to [12].

According to dominant views within cross-cultural psychology [12], there are at least three conceptions relating constructs to their contexts: relativism, absolutism, and universalism. Each implies a particular approach to the development and cross-cultural adaptation of measurement tools, as well as for establishing comparability of results arising from quantitative studies.

Relativism proposes that less tangible conditions should be understood exclusively in terms of their cultural specificities. This approach tends to reject quantitative comparisons between studies carried out in distinct contexts. Here, evaluating less concrete constructs requires using measurement tools developed exclusively for the contexts under investigation, making it difficult or indeed impossible to establish meaningful comparisons. From a practical viewpoint, adopting this perspective corresponds to being prepared to accommodate or develop a new instrument for every sociocultural context. Consistency in scientific knowledge may thus only be appraised through qualitative comparisons.

In stark contrast, the absolutist approach entirely downplays construct specificity as a result of sociocultural factors. Instead, complex phenomena are considered inherently invariant, with interpretations arising from any version of the instrument as rigidly similar, regardless of context. For example, the meaning of items reflecting OHRQoL is considered constant, irrespective of the sociocultural context. In practice, this approach presumes that comparisons of quantitative studies conducted in different sociocultural contexts are not problematic at all. It also assumes that studies may use the same measurement instruments without any prior appraisal of the cultural impact on how the underlying constructs are interpreted and, therefore, assessed. In the current example, the absolutist approach would merely recommend translating the same instrument to a range of different languages so that studies can be conducted and compared with each other.

The view set forth by the universalist approach occupies an intermediate position between the other two approaches. Accordingly, constructs are common to human life, but their expression and interpretation may still be influenced by sociocultural factors to varying degrees. The emphasis is on the use of instruments that are structurally equivalent, but adapted to the specificities of each context, whenever required. Returning to the previous example, the frequencies of low OHRQoL in Brazil and Australia could be compared through an instrument that would be equivalent in both countries. However, if we were to use this tool in a very specific context – an indigenous village in Brazil, for instance – some adaptation would be necessary for it to be applicable in this new context. Adaptation to social, linguistic, and cultural particularities may even include using items with distinct semantics or content, provided that the instrument's overall functionality is kept. This means that the adapted tool is still able to assess the construct under investigation in an equivalent way, thus allowing quantitative comparisons between investigations.

Although there is still some dispute as to which approach should be followed, scientific debates have emphasized either the relativist or the universalist perspective, poignantly dismissing the absolutist view [12].

In light of the cross-cultural approaches usually adopted in the field of oral health, we recommend following the universalist one [1, 15, 16]. Adoption of a universalist perspective leads to at least three scenarios, as depicted in Fig. 31.1, and described below [1, 17].

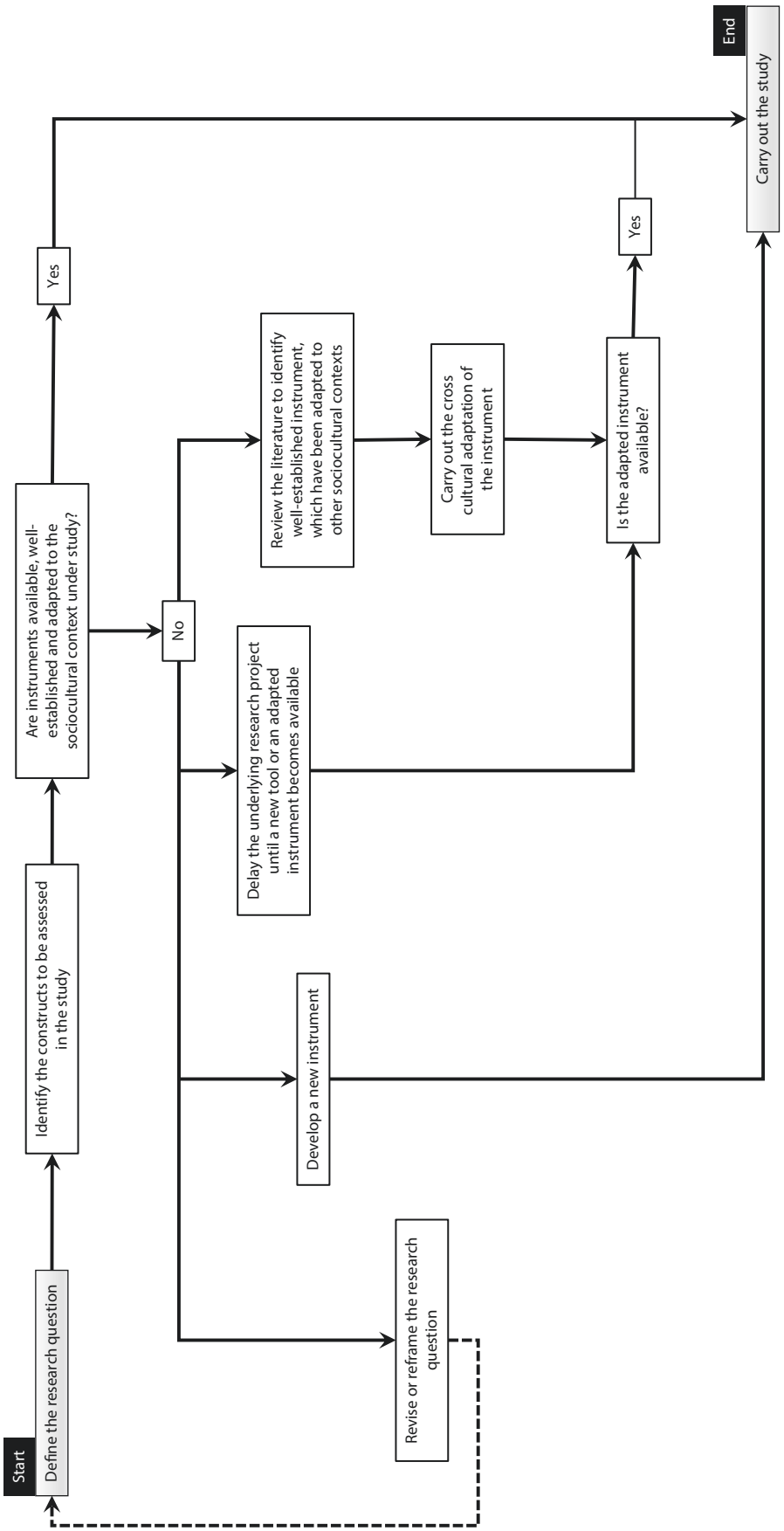


Fig. 31.1 Paths to follow when faced with three different research scenarios

Scenario 1 – when "ready-to-use" instruments are available to assess the constructs of interest. "Ready-to-use" instruments are those that are well-established, widely used, and cross-culturally adapted to a range of different contexts. A good example is the questionnaire for assessing general quality of life developed through a joint effort by WHO researchers and a group of 15 international institutions from diverse sociolinguistic-cultural contexts – WHOQOL [18].

Scenario 2 – when measurement tools are available, but their use in a given sociocultural context requires further refinement. Researchers face this scenario when an established instrument exists for measuring a construct of interest in a given setting, yet still requires cross-cultural adaptation to the new sociocultural milieu. Brazilian researchers studying OHRQoL faced this scenario some time ago. Despite the availability of a number of instruments elsewhere [19], none were available in Brazil. This is the case of the Oral Health Impact Profile, originally developed in Australia [20], which needed cross-cultural adaptation to Brazilian Portuguese before it could be used any wider in studies assessing the antecedents or consequences of oral health-related quality of life [21, 22].

Scenario 3 – when no instruments are available or those that exist have shortcomings, entailing the need to develop new measurement tools afresh. As well as the need to fully justify the inadequacy of the existing instruments, the challenge here is to advance a new tool before proceeding with the originally intended research. This is a possible but not necessarily desirable scenario. The main reason for not lightly recommending this option is that pursuing an instrument from scratch requires a considerable effort and is rather costly. Even so, pioneering research initiatives sometimes demand facing this challenge. For instance, researchers in psychiatry have recently met with this incumbency [23]. With the changes in the concept and ensuing diagnostic criteria for post-traumatic stress disorder, developing a new measurement instrument to assess the "new" construct of interest became necessary.

A broad and exhaustive literature review should be conducted to determine which of the above scenarios apply to the instruments under investigation. Four steps may be recommended to this end:

1. Identify the relevant bibliographic databases, focusing on the traditional sources in the health field, such as PubMed, as well as on those from other akin areas like psychology, education, and sociology. This range of sources increases the sensitivity of the search, especially if followed by a refinement of the terms employed in the process.
2. Identify all the instruments proposed to measure the constructs of interest. Some of these may not have been published in books or scientific articles. In such cases, searching for additional information will be important, either in the gray literature or by contacting researchers working in the fields as to their unpublished work.
3. Summarize the development trajectory of the identified tools, highlighting those with a well-established history, signaled by good indicators of validity and reliability and/or extensive use by the scientific community. Begin with summarizing more general characteristics, such as country of origin, year of publication, dimensional structure and number of items, response options, level of schooling required to understand the items, average completion time, etc. Next, compare and evaluate these and other data across all the instruments that were identified.

Figure 31.2 depicts the steps involved in either the development of new instruments or the cross-cultural adaptation of existing measurement instruments. Beyond the technical and methodological details supporting the diagram [1, 14, 15, 24, 25], the emphasis here is on the sequence of stages to be followed. Substantial literature covering this first phase strengthens what may be found in the ensuing stages. The literature review is useful not only to allowing an informed decision on which instruments to emphasize but also to identifying gaps that should be filled by future psychometric studies.

For a guide to evaluating the psychometric properties of a measurement tool, refer to the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) initiative [25, 26], as well as the insights offered in Reichenheim et al. [24].

4. Finally, select the instruments that are well suited to the research question, prioritizing those with established psychometric properties. Choices should also be informed by potential ethical, budgetary, and time constraints.

Having identified the most promising instruments for each construct, the primary study can continue. The chapter's next three subsections provide a detailed appraisal on how to proceed in each of these three scenarios.

31.3.1 What to Do When Instruments Are Available and Ready to Use (Scenario 1)

Suppose that the research question of your study refers to the frequency of dental caries and its relation to OHRQoL in the adult population of London. As argued

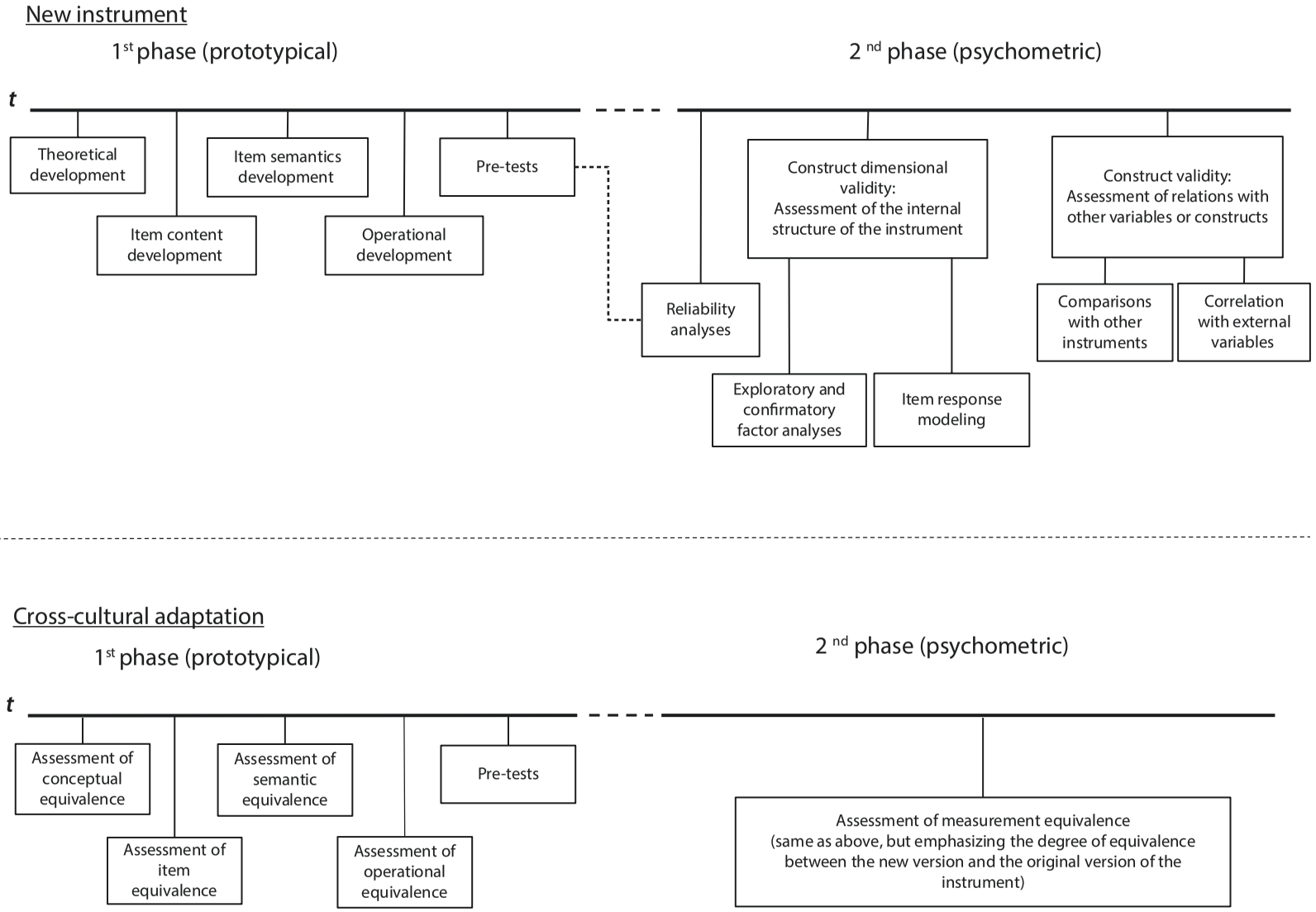


Fig. 31.2 Main stages concerning the development or cross-cultural adaptation of instruments

in the previous section, dental caries is an oral health condition that can be directly measured, as opposed to OHRQoL. This does not imply, however, that an in-depth review of the most up-to-date techniques for assessing dental caries should not be undertaken during the study planning. Quite the opposite; care should be taken when choosing the strategies to measure tooth decay, giving precedence to those that attain a high-quality measure and, by extension, those allowing comparisons with studies with a similar aim. Rigor must also be applied in the assessment of OHRQoL.

In case an adapted version of the instrument with good psychometric properties is available, it should be included in the multi-thematic questionnaire without further ado. Although this scenario requires less effort than those discussed in the next two subsections, the research team needs to pay attention to other important issues in the planning and execution of the study on dental caries and OHRQoL.

Various operational questions relating to assembling the instruments to be used also need prioritizing. This includes refining the sequence of modules, mode of administration (face-to-face interviews, self-completed questionnaires or online forms, contact by telephone, etc.), and the time needed to complete an interview. Questionnaires addressing a large number of constructs tend to be lengthy, potentially reducing the interest and availability of respondents, and thus negatively affecting the quality of the data. A detailed account of these and other issues may be found in several external publications [27–29].

Next, the multi-thematic questionnaire needs to be tested in conditions similar to the primary research for which it was intended. Note, however, that the procedures relating to the development or cross-cultural adaptation process do not apply here since the instruments under review are "ready to use." The focus is not on the refinement of one or more tools comprising the multi-thematic questionnaire, but rather on how they fit and perform together. If, nonetheless, problems arise in one or more constituent tools – for example, in terms of comprehension or acceptability of certain items – the research team will have to step back and reevaluate the situation. Clearly, this involves more complex procedures, as described in the following sections. If no problems are detected, the next step consists of piloting the main study in which real data collection conditions will be tested. The aim is to evaluate whether all the operational details proposed in the planning stages are ready to be implemented.

Getting the multi-thematic questionnaire up and running at the start of the data collection is only one task to be accomplished. Quality control strategies will have to be devised for the data collection period as well, not least to assess the reliability of all component instruments (especially with regard to their temporal stability). Although preliminary tests carried out at the planning and setup stages may have cleared the way for further use, real data collection conditions may turn out important and unanticipated problems that need dealing with instantly [27].

31.3.2 Recommendations When Instruments Are Available, but Their Use in the Given Sociocultural Context Requires Additional Work (Scenario 2)

A detailed literature search may also reveal the following setup: an instrument is available but not yet adapted for use in the new context. For instance, the adaptation of the Oral Health Impact Profile took place in different periods, an earlier [22] and a more recent one [21]. These publications show us that the adaptation process is never completed and may always be updated or resumed to explore additional features or properties not addressed so far.

Of note, care should be taken to identify those instruments developed in a specific language in the past or in a country speaking the same language, but distinct from a sociocultural point of view. One question that arises is whether there is a need to engage in a "cross-cultural" adaptation process in these cases, given the apparent cultural similarities. The answer involves knowing both contexts, especially with regard to their sociocultural particularities and their impacts on the construct of interest. This knowledge can be obtained through a broad literature review on the subject. Qualitative studies employing, among other techniques, in-depth interviews [30] or focus groups [30, 31] may also be informative to gain a better understanding of both contexts of investigation.

As mentioned in the previous section, the research team very often faces a situation in which the primary study needs to be deferred so that the measurement instrument can be adapted to the new context. For this scenario, we provide some recommendations concerning the steps to be taken, as well as to the procedural guidelines to be followed in the cross-cultural adaptation of an instrument. The related literature proposes alternative strategies [14, 32–36]. Here we opt for an operational model taken from Herdman et al. [13, 14] comprising five interrelated stages. Depicted in Diagram 2, the model is summarized in ◘ Table 31.1. Further details may be found in an earlier publication [15].

According to this model, the first stage entails evaluating conceptual equivalence, i.e., whether there is any connection between the definitions advanced in the original and target context with respect to the construct. In the second stage, item equivalence is assessed through an appraisal of the component items' pertinence in the new

Table 31.1 Cross-cultural adaptation stages of measurement instruments

Type of equivalence to be assessed	Strategies to undertake
Conceptual equivalence	Literature review on the sociocultural context for which the instrument was originally developed, as well as on the new target population Discussion with panel of experts Discussion with target population
Item equivalence	Discussion with panel of experts Discussion with target population
Semantic equivalence	Translation Back translation Assessment of semantic equivalence between the original instrument and the instrument that was back translated Discussion with panel of experts Discussion with target population to fine tune the wording of the items Pretesting of new version of the instrument
Operational equivalence	Assessment of pertinence, mode of administration, acceptability, etc.
Measurement equivalence	Psychometric studies to assess the instrument's validity and reliability

sociocultural context (Table 31.1). Such an appraisal takes place in light of a thorough literature review on the development of the original instrument. As well as learning about the respective concepts and definitions, this stage aims to assess the decision-making processes guiding the choice of items. Members of the new context may also be involved in the process, either through individually based, open, or semi-structured interviews [27, 30] or through group approaches, such as focus groups [30, 31].

Evaluating semantic equivalence comprises the third stage. This involves exploring the ability to transfer the meaning implied in the original wording to the adapted version, as well as checking whether the items achieve a similar effect on respondents of the new domain [14]. The process begins with translating the original instrument into the target language (culture). Preparing two or more versions independently is always advisable. This will expand the possibilities for choosing terms when consolidating the final edition of the instrument in a later stage. The versions are then back translated by other translators, again working independently. Good practice recommends translations to be carried out by professionals whose mother tongue pertains to the target population, while back translations are effected by professionals from the culture (language) of origin.

Next, a separate arbiter formally evaluates whether the reversed translations and the original version are equivalent. The main goal is to check if any of two or both tiers of meaning are retained. One comprises denotative (referential) meaning and concerns the ideas or objects to which the constituent words refer [14]. Equivalence in referential meaning is deemed sustainable if there is a literal correspondence between words in both languages. Connotative (general) meaning concerns the second tier. The focus is on the wider impact an item wording may convey in the new setting. The appraisal centers on the intensity and emotional (affective) load as perceived by respondents. This assessment is necessary because a literal, word-for-word (denotative) correspondence of a given term may not always put an item on a par across cultures. To achieve an overall equivalence, fine-tuning may be required. To this end, it is sometimes worth stepping back and returning to the target population to accrue more insight, for instance, by organizing additional ad hoc focus groups [30, 31].

The following step of semantic evaluation involves the same expert group engaged in the assessment of conceptual equivalence. The aim is to identify and deal with problems arising in the previous stages. The final goal here is to develop and propose a compiled version, either by incorporating items derived from one of the available translations *as is* or by modifying wording and possibly content in the light of the finding gauged before.

Pretesting the proposed version (the translated prototype) is an important last step. Testing the selected instruments on respondents holding a similar profile to the population of interest allows checking several aspects and settles on some alternatives arising in the process. Pretests are useful to evaluate the order of items, the time needed for instrument completion, acceptability, comprehension, and emotional impact. Detailed accounts on the various formats and uses of pretests may be found elsewhere [27, 29, 37], viz., the use of techniques to check the understanding of specific items (e.g., cognitive interviews [38]). Pretests should be accompanied by meetings of the research team.

The fourth stage concerns the evaluation of operational equivalence. This refers to the possibility of utilizing an instrument similarly to the original, with particular attention as to whether instructions to the respondent or interviewer, setting, and the mode of administration sought in the original instrument may be kept in the adapted version. In this stage, the response options should also be inspected, attuning the respective semantics to the target population. For example, if an instrument is initially designed to be self-completed by fully educated respondents, fine-tuning may be required to be able to apply it through face-to-face interviews if the target population is of low schooling. Rephrasing items (as

discussed in the previously described stage) and reducing the number of options might be necessary to improve comprehension and enable more accurate responses.

The process finishes with an assessment of measurement equivalence. This stage investigates the psychometric properties of the new version (prototype) by systematically comparing its findings to those obtained for the original version. Measurement equivalence is evaluated appraising reliability and validity. Note that the notion of equivalence takes center stage here since the aim is to assess how close the new version comes to the original. As indicated in a previous section, moving forward to adapt an instrument presumes a positive account of its psychometric history, with high levels of validity and reliability being expected anyway.

Of note, the assessment of measurement equivalence is complex and lengthy and should not be underestimated. Some aspects relating to the psychometric analyses of measurement instruments are examined in the following section, but since they apply equally to cross-cultural adaptation processes, we take the opportunity to indicate references which the reader may consult for more in-depth accounts [1, 6, 15, 24, 39, 40].

31.3.3 Procedures When No Instruments Are Available or Those That Exist Are Insufficient, Requiring the Development of New Ones for the Underlying Research to Be Conducted (Scenario 3)

Among the suggested scenarios, this is the most demanding on the researcher. A rigorous literature review may indicate that instruments to assess one or more constructs delimited by the research question are absent or that some tools are available but fall short of minimal standards. Undertaking this review is no easy task, not even for an experienced researcher.

> Therefore, extra care should be taken when deciding to embark in the development of a completely new instrument. Without due procedural rigor, subsequent use of a new tool may produce quantitative data lacking comparability across studies, ultimately leading to undue wastes in financial, material, and other human precious resources.

Still, there are situations where a new instrument is justifiable and should be pursued. When successful, developing new measurement tools has considerable potential to produce original insights and advance scientific knowledge. The downside is that sometimes this course of action requires delaying the underlying research project until a new tool becomes available. Researchers tend to prioritize keeping the original research project going, either for financial and operational reasons or due to academic pressure. The consequences can be damaging if a particular construct ends up being misrepresented by a limited set of quickly installed items or worse, through a single ad hoc item. The message is clear: even though admittedly a burden on expediency, the nocuous consequences of bypassing this important step should not be minimized.

Below is a brief appraisal of the main steps to be followed in the development of a new instrument. Again, we recommend reading other references for a more detailed exploration of the question [1, 4, 5, 6, 16, 41]. Based on the model illustrated in Diagram 2, Table 31.2 succinctly presents all stages of the process.

As conveyed in Table 31.2, the endeavor starts with the (re)evaluation of the constructs of interest. Only then may the potential items be suggested and drafted. Even in the case one is developing a new instrument, it is good practice to revisit the literature review

Table 31.2 Stages of instrument development

Stage	Strategy to undertake
Define the concepts to study and their respective dimensions	Literature review Examination of the theoretical model of the study
Suggest items that reflect each of the studied dimensions	Literature review Discussion with researchers, other experts on the topic, and members of the target population
Select items that will compose different sets of items (prototypes)	Discussion with researchers and other experts on the topic
Define the scoring system/the response options	Discussion with researchers and other experts on the topic
Define item wording	Researchers
Pretests	Administration of the various instrument prototypes to members of the target population
Assessment of psychometric properties of each item set	Validity and reliability studies
Selection of the final instrument	Discussion with researchers and other experts on the topic
Corroboration studies	Use of the instrument in other research contexts

that pointed to the current inadequacies and motivated this path in the first place. This avoids repeating mistakes and problems found so far. However, it is not simply about plugging in old items into this new instrument. Keep in mind that items are not meant to function through their nominal meaning (i.e., their explicit content), but rather as manifests of the underlying latent construct, mapping specific positions along the trait's increasing gradient of intensity [4]. Therefore, items must not be interpreted in isolation, but always in tandem.

Next, the aim is to identify those items that best represent the concepts of interest. To widen the choices as much as possible, different sets of items should be proposed. The main challenge is to come up with a set that enhances content validity, yet is not so large as to negatively affect the measurement tool's acceptability and applicability.

Identifying and specifying this set of items requires paying attention to scalability. As hinted before, valid instruments must be capable of positioning respondents along a certain *continuum* of intensity by assigning specific values to them. The literature on the topic is rich in techniques and strategies aimed at defining response options (e.g., visual analog scales, adjective scales, Likert scales, semantic differential scales) and selecting the best items (e.g., Thurstone or Guttman method) [6, 28, 29].

Improvement and semantic fine-tuning of the selected items then need to be carried out. Wording that is objective, clear, simple, and kept as short as possible tends to avoid ambiguity and should always be sought. Preference should be given to items that are easy to understand, harmonious in relation to the culture in question, and without jargon, slang, or unnecessary sophistication. This stage also involves some fieldwork in which a first batch of alternative versions is subjected to intensive evaluation regarding its acceptability, comprehension, and emotional impact. Based on evidence from this pretest, the more promising versions may be chosen.

The ensuing step covers the psychometric studies. These should examine the items in terms of relevance to the constructs and respective dimensions, establish the scales they form, and identify cutoff points, among other aspects. This is an iterative process rather than a sequential endeavor of self-contained evaluations covering each feature at a time.

Several strategies or techniques may be used to assess reliability, among which we highlight the Cronbach's alpha coefficient [42] and other alternatives [43, 44], as well as the correlation between the total score and each item [45]. Intra- and interobserver reproducibility also needs checking. A range of methods of analysis are available to assess agreement, such as the Cohen's kappa coefficient [46]; the estimators proposed by Feinstein and Cicchetti [47]; the vast gamut of intra-class correlation coefficients [48]; the Lin's concordance coefficient [49]; and the Bland and Altman method [50]. Repeated reliability analyses over the course of a research program may also add support to either endorse or reject a particular instrument in the long run.

Multiple strategies have been suggested to establishing scales based on items. The most common is simply to add up component items' raw scores. This simple operation, however, does not allow us to contemplate the nuances and relative importance of each item. This requires weighing procedures, such as transformations by means of percentiles, standardization or normalization [6], or specification of interval scores via modeling procedures such as multiple regression or item response theory/Rasch models [51, 52].

In the process of conceiving and consolidating a new instrument, formal validation studies need to be carried out. Mind that when an instrument is considered apt to undergo psychometric evaluations, face validity is presumed a priori [6]. However, this is insufficient. More in-depth studies are required to corroborate this type of validity.

Implicit in Diagram 2, the COSMIN initiative subdivides validity into "internal" and "external" validity [25, 26]. "Internal" validity relates to the instrument's latent structure. Generally speaking, this type of validity is evaluated through multivariate methods, e.g., factor analytic [39], item response theory [51], latent class [52], or mixture [53] models. A range of psychometric properties needs to be examined, including the number of dimensions/factors; item reliability (factor loadings); item-to-factor specificity (cross-loadings); correlations between residual variances that may indicate item redundancy (residual correlations); factor-based convergent and discriminant validity; and/or scalability [24, 39].

Assessing "external" validity, in turn, has much to do with testing associations between the construct of interest and other variables or concepts to which it should or should not be related. The comparisons may be carried out within the scope of the construct itself, or involve other concepts, attributes, and characteristics linked to the general theory in which this is inserted [6].

In the first approach, the new instrument is compared with similar instruments available in the scientific literature. When no standard instrument exists, one evaluates the correlations between the scale and instruments assessing the common construct. This approach is related to studies aiming to develop a shorter version of an instrument, yet striving for good measurement capabilities. The existence of a standard instrument or procedure enables studying concurrent/criterion validity.

Streiner et al. [6] distinguish concurrent validity from predictive validity, classifying both as criterion validity. Assessment of criterion validity is usually based on estimates of sensitivity and specificity [6, 54].

Studies covering the second approach vary enormously, spanning from simple exploration of bivariate relations (correlations) between the construct and other factors to complex epidemiological studies. The common premise is that confirming hypothesized associations lends credence to the instrument's external validity. Hence, it should be stressed that studying an instrument's external validity also implies studying the underlying theory itself, within cycles of conjectures and refutations/corroborations. External validity entails a continuous process through which the degree of credibility to be given to an inference is determined through "reading off" from a numerical scale [6].

The process for evaluating the quality of a new instrument is clearly not exhausted in the first study. Even if initial evidence is promising and suggests validity, it is essential that its performance in other contexts is sought further.

An instrument needs to be continually subjected to critical appraisal by interested peers. The vast range of details and options, many intrinsically subjective, demands that the refinement of the any new measurement tool rests upon continuous debates and negotiations among peers.

31.4 Conclusions

In concluding the present chapter, we hope to have highlighted the role of measurement instruments in the field of oral epidemiology. The idea of quantitative comparability was a common axis across all subsections, such that the consistency of findings originating from studies carried out in different sociocultural contexts may help consolidate scientific knowledge. We advise a universalist perspective in the production of quantitative epidemiological evidence and, in parallel, its precedence in cross-cultural adaptations of instruments. The principles and concepts explored in this text apply not just to measurement of less tangible constructs but also to directly observable conditions, such as cephalometric measurements, the number of natural teeth, and so on. Our hope is that the reading of this text and the cited references contributes to a greater development of oral epidemiology and its capacity to generate scientific evidence that will transform our current and future sociocultural contexts.

References

1. Reichenheim ME, Moraes CL. Qualidade dos instrumentos epidemiológicos. In: Almeida-Filho N, Barreto ML, editors. Epidemiologia & saúde: fundamentos, métodos e aplicações. Rio de Janeiro: Guanabara Koogan; 2012. p. 150–64.
2. Porta M. A dictionary of epidemiology. Oxford: Oxford University Press; 2014.
3. Evans AS. Causation and disease: a chronological journey – the Thomas Parran lecture. Am J Epidemiol. 1978;108(4):249–58.
4. Wilson M. Constructing measures: an item response modeling approach. Mahwah: Lawrence Erlbaum Associates; 2005.
5. DeVellis RF. Scale development: theory and applications. Thousand Oaks: Sage Publications; 2003.
6. Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. Oxford: Oxford University Press; 2014.
7. Atchinson KA. Understanding the quality in quality care and quality of life. In: Inglehart MR, Bagramian RA, editors. Oral health-related quality of life. Hannover Park: Quintessence Books; 2002. p. 21–30.
8. Pett MA, Lackey NR, Sullivan JJ. Making sense of factor analysis: the use of factor analysis for instrument development in health care research. Thousand Oaks: Sage Publications; 2003.
9. Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol. 1997; 25(4):284–90.
10. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58(5):295–300.
11. Popper K. The logic of scientific discovery. New York: Routledge; 2005.
12. Berry JW, Poortinga YH, Segall MH, Dasen PR. Cross-cultural psychology: research and applications. New York: Cambridge University Press; 2007.
13. Herdman M, Fox-Rushby J, Badia X. 'Equivalence' and the translation and adaptation of health-related quality of life questionnaires. Qual Life Res. 1997;6(3):237–47.
14. Herdman M, Fox-Rushby J, Badia X. A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. Qual Life Res. 1998;7(4):323–35.
15. Reichenheim ME, Moraes CL. Operacionalização de adaptação transcultural de instrumentos de aferição usados em epidemiologia. Rev Saude Publica. 2007;41(4):665–73.
16. Reichenheim ME, Moraes CL. Desenvolvimento de instrumentos de aferição epidemiológicos. In: Kac G, Sichieri R, Gigante DP, editors. Epidemiologia nutricional. Rio de Janeiro: Fiocruz/Atheneu; 2007. p. 227–43.
17. Bastos JL, Duquia RP, González-Chica DA, Mesa JM, Bonamigo RR. Field work I: selecting the instrument for data collection. An Bras Dermatol. 2014;89(6):918–23.
18. World Health Organization. The World Health Organization quality of life (WHOQOL). Geneva: World Health Organization; 2012.
19. Locker D, Allen F. What do measures of 'oral health-related quality of life' measure? Community Dent Oral Epidemiol. 2007;35(6):401–11.
20. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health. 1994;11(1):3–11.
21. dos Santos CM, Oliveira BH, Nadanovsky P, Hilgert JB, Celeste RK, Hugo FN. The Oral Health Impact Profile-14: a unidimensional scale? Cad Saude Publica. 2013;29(4):749–57.

22. Oliveira BH, Nadanovsky P. Psychometric properties of the Brazilian version of the Oral Health Impact Profile–short form. Community Dent Oral Epidemiol. 2005;33(4):307–14.
23. Weathers F, Litz B, Keane T, Palmieri P, Marx B, Schnurr P. The PTSD checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD. US Department of Veteran Affairs: Washington DC, 2013.
24. Reichenheim ME, Hökerberg YHM, Moraes CL. Assessing construct structural validity of epidemiological measurement tools: a seven-step roadmap. Cad Saude Publica. 2014;30(5): 927–39.
25. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, Bouter LM, de Vet HCW. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res. 2010;19(4):539–49.
26. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, Bouter LM, de Vet HC. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol. 2010;63(7):737–45.
27. Bowling A. Research methods in health: investigating health and health services. Maidenhead: McGraw-Hill; 2014.
28. Converse JM, Presser S. Survey questions: handcrafting the standardized questionnaire. Quantitative applications in the social sciences. Thousand Oaks: Sage Publications; 1986.
29. Moser C, Kalton G. Survey methods in social investigation. London: Heinemann; 1972.
30. Gaskell G. Entrevistas individuais e grupais. In: Bauer WB, Gaskell G, editors. Pesquisa qualitativa com texto, imagem e som: um manual prático. Petrópolis: Vozes; 2002. p. 64–89.
31. Krueger RA, Casey MA. Focus groups: a practical guide for applied research. Thousand Oaks: Sage Publications; 2000.
32. Behling O, Law KS. Translating questionnaires and other research instruments: problems and solutions, vol. 133. Thousand Oaks: Sage Publications; 2000.
33. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol. 1993;46(12): 1417–32.
34. Perneger TV, Leplège A, Etter J-F. Cross-cultural adaptation of a psychometric instrument: two methods compared. J Clin Epidemiol. 1999;52(11):1037–46.
35. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine. 2000;25(24):3186–91.
36. Kristjansson EA, Desrochers A, Zumbo B. Translating and adapting measurement instruments for cross-linguistic and cross-cultural research: a guide for practitioners. Can J Nurs Res. 2003;35(2):127–42.
37. Fowler FJ. Improving survey questions: design and evaluation. Applied social research methods series. Thousand Oaks: Sage Publications; 1995.
38. Willis GB. Cognitive interviewing: a tool for improving questionnaire design. Thousand Oaks: Sage Publications; 2004.
39. Brown TA. Confirmatory factor analysis for applied research. Methodology in the social sciences. New York: Guilford Press; 2015.
40. HairV JF Jr, Black WC, Babin BJ, Anderson RE. Multivariate data analysis. London: Pearson; 2010.
41. Reichenheim ME, Moraes CL. Buscando a qualidade das informações em pesquisas epidemiológicas. In: Minayo MCS, Deslandes SF, editors. Caminhos do pensamento: epistemologia e método. Rio de Janeiro: Fiocruz; 2002. p. 227–54.
42. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297–334.
43. McDonald RP. Test theory: a unified treatment. Mahwah: Lawrence Erlbaum Associates; 1999.
44. Raykov T. Scale reliability, Cronbach's coefficient alpha, and violations of essential tau-equivalence with fixed congeneric components. Multivar Behav Res. 1997;32(4):329–53.
45. Nunnally JC. Psychometric theory. McGraw-Hill series in psychology. New York: McGraw-Hill; 1967.
46. Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas. 1960;20(1):37–46.
47. Feinstein AR, Cicchetti DV. High agreement but low kappa: I. the problems of two paradoxes. J Clin Epidemiol. 1990;43(6): 543–9.
48. Shrout PE. Measurement reliability and agreement in psychiatry. Stat Methods Med Res. 1998;7(3):301–17.
49. Lin LIK. A concordance correlation coefficient to evaluate reproducibility. Biometrics. 1989;45(1):255–68.
50. Martin Bland J, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;327(8476):307–10.
51. Wilson M. Constructing measures. An item response modeling approach. Mahwah: Lawrence Erlbaum Associates, Publishers; 2005.
52. Collins LM, Lanza ST. Latent class and latent transition models. Hoboken: WIley & Sons; 2010.
53. Clark SL, Muthén B, Kaprio J, D'Onofrio BM, Viken R, Rose RJ. Models and strategies for factor mixture analysis: an example concerning the structure underlying psychological disorders. Struct Equ Model Multidiscip J. 2013;20(4):681–703.
54. Fletcher RH, Fletcher SW, Fletcher GS. Clinical epidemiology: the essentials. Philadelphia: Lippincott Williams & Wilkins; 2012.

Further Reading

As a resource for further learning, we recommend the following bibliographic references to interested readers. The last two references also touch upon the topic of sample size and power:

Epstein J, Santo RM, Guillemin F. A review of guidelines for cross-cultural adaptation of questionnaires could not bring out a consensus. J Clin Epidemiol. 2015;68(4):435–41.
Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Health. 2005;8(2):94–104.
Carmines EG, Zeller RA. Reliability and validity assessment. Thousand Oaks: Sage; 1979.
Furr RM. Scale construction and psychometrics for social and personality psychology. London: Sage; 2011.
Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. Oxford: Oxford University Press; 2014.
Brown TA. Confirmatory factor analysis for applied research. Methodology in the social sciences. New York: Guilford Press; 2015.

Reproducibility and Validity of Diagnostic Tests

Renato Pereira da Silva, Andréa Videira Assaf, and Antonio Carlos Pereira

Contents

32.1 Introduction – 480

32.2 Reproducibility of Diagnostic Tests – 480
32.2.1 Percentage of Agreement – 480
32.2.2 Kappa Statistics – 481
32.2.3 Intraclass Correlation Coefficient – 484
32.2.4 Dice Index – 485

32.3 Validity of Diagnostic Tests – 486
32.3.1 Sensitivity and Specificity – 487
32.3.2 Predictive Values – 487
32.3.3 Likelihood Ratios – 487
32.3.4 False-Positive Rate (FPR) and False-Negative Rate (FNR) – 488
32.3.5 Correct Classification – 488
32.3.6 Youden's J Statistic – 488
32.3.7 Diagnostic Odds Ratio – 488
32.3.8 Receiver Operating Characteristic Curve – 489
32.3.9 Bayes' Theorem – 490

32.4 Final Considerations – 492
32.4.1 Outlook – 492
32.4.2 Closing Remark – 492

References – 493

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_32

Learning Objectives

- Concepts of validity and reproducibility
- Main statistical tools
- Future trends in validity and reproducibility studies

Core Message

- Higher values of reproducibility and validity simultaneously are sine qua non conditions for the success of a diagnostic test.
- The weighted Kappa statistic is a reproducibility measure recommended as the first choice for evaluating nominal data in epidemiological studies such as dental caries diagnostic studies.
- The intraclass correlation coefficient is a reproducibility measure indicated for test-retest studies and for intra- and inter-examiner agreement studies (considering numerical continuous data).
- Concomitant use of several validity measures gives a complete overview of the diagnostic tests.
- The use of ROC curve and area under curve enables the easy and fast comparison of different diagnostic methods.

32.1 Introduction

Every day, dentists are faced with making clinical decisions in their dental office, with a view to obtaining the best outcome to each clinical condition identified. In parallel, public oral health service managers plan, implement, and evaluate interventions in public health. In both cases, detecting, diagnosing, and monitoring illnesses and oral diseases represent significant factors in the successful outcome of the actions of these professionals. In view of the foregoing, this makes the use of valid diagnostic tests a sine qua non for achieving the expected success. Therefore, researchers play a fundamental role in the most diverse areas of dentistry, in view of the epidemiological, demographic, and nutritional transitions occurring in the development of diagnostic technologies (diagnostic tests) that are reproducible and valid for the early diagnosis of diseases that affect the stomatognathic system. The conscientious use of trustworthy diagnostic tests is pointed out as also being responsible for the reduction in the risk of iatrogenic damage occurring in individuals and unnecessary financial expenditure, notably within the scope of public health.

But after all, what is a valid diagnostic test? How can it be identified? How must it be adequately used and interpreted? The aim of this chapter is to enlighten readers about these questions, helping them in their choices as regards the use of diagnostic tests suited to their purposes, whether they are for clinical purposes or directed toward the development of different types of researchers, from the study of methods for estimating reproducibility and validity of these tests.

32.2 Reproducibility of Diagnostic Tests

The first methodological aspect of a diagnostic test to be considered by professionals with regard to its development or adoption is its capacity to produce similar results when repeated measures are made under laboratory, clinical, or epidemiological conditions. Thus, its reproducibility, reliability, repeatability, agreement (intra- and inter-rater/examiner), consistency, stability, trustworthiness, or precision are demonstrated [1, 2].

The measurement of reproducibility must be used to observe the constancy of results provided by a technological appliance or by the diagnostic response of a group of evaluators or examiners. We can exemplify the two cases, by focusing on the detection of carious lesions. If we use an auxiliary test, such as the DIAGNOdent®, which is based on qualitative measurement by means of laser light, this appliance, because it is indicated as being an adequate technology for professional use, must present good reproducibility or diagnostic constancy; that is, the analysis of teeth with or without caries, under the same clinical or laboratory conditions, must demonstrate the same numerical results repeatedly [3]. This reproducibility must also be shown when a single test is performed, such as when an exam for dental caries is performed by various examiners under clinical or epidemiological conditions. After a stage of training and calibration of these individuals, the improvement in diagnostic precision has been observed, which is of great value to avoid diagnostic responses that generate under- or overestimation of the disease [4–6].

32.2.1 Percentage of Agreement

The *percentage of agreement* (*general percentage of agreement*; *simple agreement*; *percentage agreement*; *PA*) is the simplest way of measuring and interpreting the reproducibility between the diagnostic tests performed by a single examiner in two or more calibration sessions (intra-examiner consistency) or between two or more examiners in one and the same calibration session (inter-examiner consistency) [2, 6]. In *PA*, the degree of agreement is given by the ratio between the number of coincident diagnoses related to a determined disease in oral health and the total number of diagnoses of this oral condition. However, the *PA* is influenced by random errors (chance; errors resulting from inadequate sample size, by biological variance of the subjects studied, and low prevalence of the clinical condition under study in the population sample) and systematic errors

(intrinsic subjectivity of the examiner; conditions for performing the exams; natural wear of the instruments and appliances used) [6, 7]. These factors occur for a possibly distorted PA value. Therefore, whenever possible, more consistent statistical methods for measuring the reproducibility of diagnostic tests are recommended.

32.2.2 Kappa Statistics

Kappa statistic (*Kappa coefficient*, *Cohen's Kappa*; κ), because of their potential to control the negative effects of random errors on reproducibility, has been recommended as the alternative of first choice, notably in epidemiological studies with nominal data[6,8]. Therefore, the Kappa statistic expresses the proportion of agreement observed, which is not due to chance, in relation to the maximum agreement that would occur beyond chance. Thus, its values range from "-1" (total disagreement), passing through "0" (agreement due to chance) up to "+1" (total agreement, disregarding chance) [8, 9]. The Kappa statistic may be calculated both my means of statistical programs, for example, "Statistical Analysis System" (SAS®), "IBM's Statistical Package for the Social Sciences" (SPSS®) or STATA®, and manually. For manual calculation, the initial step is the construction of a square matrix (contingency table) 2×2, 3×3, 4×4... n×n, where the examiners' data will be recorded (Table 32.1).

From the conditions recorded in this contingency table, calculation of the Kappa statistic proceeds by means of the following formula:

$$K = \frac{P_o - P_e}{1 - P_e}$$

where P_o = proportion of agreements observed

$P_o = (a + e + i) \div n$

P_e = proportion of agreements expected

$$P_e = \{(a + b + c) \times (a + d + g)\} + \{(d + e + f) \times (b + e + h)\} + \{(g + h + i) \times (c + f + i)\} \div n$$

After calculating the Kappa, this value is qualitatively classified with the use of a standard scale. The presence of varied classification scales has been found, because they are important tools for guiding professionals and researchers, in spite of being arbitrary both in nature and in their choice by individuals. However, according to Gwet [10], both the Landis and Koch [9] and Altman's [11] benchmark scales are acceptable. The Landis and Koch [9] benchmark scale is recommended by the WHO [6] for epidemiological studies. Furthermore, according to Gwet [10], the Fleiss benchmark scale deserves special attention due to the unduly large width of its benchmark intervals. For example, the fair-to-good range of values goes from 0.4 to 0.75 and is too broad to be very helpful in practice. Moreover, the two words "fair" and "good" have meanings that are too different for them to be lumped into a single category. "Fair" generally means it could get much better, while "good" is always considered satisfactory. If an inter-examiner reproducibility of 0.75 may be deemed acceptable, very few people will admit an inter-examiner reproducibility of 0.4 as being acceptable.

The Kappa statistic does not consider the degree of agreement or disagreement between the observers, and therefore all the disagreements are treated in a uniform manner. Thus, when the categories of the clinical conditions found are disposed in a scale (ordinal data, e.g., stages of a disease, levels of severity; total hit × partial hit × error), the use of the weighted Kappa (Kappa with quadratic weights) is recommended, with attribution of different weights for the disagreements observed, to obtain a trustworthy reproducibility, instead of the simple Kappa [7]. Generally, the values for reproducibility obtained from the weighted Kappa coincide with the values obtained by the *intraclass correlation coefficient* [1].

Table 32.1 Diagnostic test performed by two examiners

Examiner #1		**Examiner #2**			**Total**
		Clinical conditions[a]			
		0	**1**	**2**	
Clinical conditions[a]	**0**	a	b	c	a + b + c
	1	d	e	f	d + e + f
	2	g	h	i	g + h + i
	Total	a + d + g	b + e + h	c + f + i	N

[a]The number of clinical conditions will depend on the index adopted

32.2.2.1 Tendencies in Studies About the Reproducibility of Tests for Dental Caries Detection

As is the case with PA, the Kappa statistic is also affected by the prevalence of the disease in the sample of the studied population. Therefore, careful selection with regard to both number and distribution of the representative disease in the population, as well as subjects for composing the sample in reproducibility studies, is also necessary for the Kappa statistic [4, 12].

As a way of exemplifying and achieving better understanding of the abovementioned findings, the main points of some studies that investigated this statistical measure in dental caries disease will be described, with respect to clinical criteria, such as the methods for detection of lesions.

In the scientific literature, the sample size for reproducibility studies in dental caries has been verified to vary between 10 and 25 subjects, evaluated by a maximum number of 5 examiners, with a view to facilitating the discussion and diagnostic consensus among them [4, 5]. Considering dental caries, Tonello et al. [12] affirmed that the smallest size of a sample to obtain trustworthy results would be 12 subjects (individuals or teeth, depending on the aim of the study), under a prevalence of 60% of the disease in the sample, capable of simultaneously producing high *PA* (90.91%) and Kappa values (81.36%; CI = 53% to 100%), and the smallest difference between these 2 measurements ($PA - \kappa = |90.91| - |81.36| = |9.55|$). The sample of 15 subjects, under a prevalence of 30%, also produced an interesting result: $PA - \kappa = |9.14|$; however, with a $PA = 83.72\%$, $\kappa = 92.86\%$, and CI = 53% to 100%. However, when the smallest sample size is considered, high values of *PA* and κ simultaneously, smaller difference "$PA - \kappa$," and lower CI for the Kappa statistic, the authors reported that a virtual sample of 60 subjects, under a prevalence of 50% of the disease in the sample, would be more adequate to obtain a trustworthy result in a reproducibility study of diagnostic tests.

Another relative situation for conducting reproducibility studies, considering dental caries, involves filling out of the clinical record charts proposed in the *Oral Health Surveys: Basic Methods* [6]. The record of clinical conditions of third molar teeth (boxes 45, 60, 77, and 92 of the World Health Organization: Oral Health Assessment Form for Adults) of individuals in age ranges in which these teeth are invariably found erupted, or even impacted, would consist of a sequence of code "8" (unerupted tooth) in the boxes with reference to these teeth, contributing to an "artificial" increase in the inter- or intra-examiner agreement measured by the PA and also by the Kappa statistic. Disregarding the record of the clinical condition of this group of teeth could be an alternative for obtaining a more trustworthy reproducibility.

Dichotomization of the clinical conditions found, for example, grouping of codes "1" and "2" of the WHO diagnostic criteria [6], as "caries," and the others as "non-caries," although it would facilitate the calculation of reproducibility, would also produce values differing from those found by means of using non-dichotomized values, under the weighted Kappa, as will be observed in Table 32.2, as follows:

In the example (Table 32.2), the simple and weighted Kappa were used to measure the reproducibility among 3 professionals evaluating a sample of 13 individuals, representing a total of 364 permanent teeth examined (1664 tooth surfaces examined), under the diagnostic criterion recommended by the WHO [6], adapted for recording initial caries lesions in the tooth enamel surface. As observed in Table 32.2, dichotomization of the clinical conditions found showed a lower Kappa value, which could suggest that this type of measurement was not the best way of measuring reproducibility for dental caries by means of the clinical exam. We emphasize that the simple Kappa is indicated when there are only two diagnostic categories (in this example "with caries" and "without caries"), while the weighted Kappa is indicated when there are more than two categories (in the example "with caries," "with initial carious lesion," "restored with caries," "restored with initial carious lesion," "without caries," etc.).

Table 32.2 Simple × weighted Kappa values

Pairs of examiners	Non-dichotomous data (original data)				Dichotomous data	
	Simple Kappa	95% CI	Weighted Kappa	95% CI	Simple Kappa	95% CI
Exam 1*Exam 2	0.8268	0.7853–0.8684	0.8221	0.7676–0.8767	0.8199	0.7608–0.8790
Exam 1*Exam 3	0.8183	0.7765–0.8600	0.8239	0.7699–0.8779	0.7925	0.7323–0.8527
Exam 2*Exam 3	0.8714	0.8357–0.9071	0.8822	0.8402–0.9241	0.8396	0.7843–0.8949
Kappa (mean)	*0.8388*		*0.8427*		*0.8173*	

In addition to the abovementioned, non-observation of prevalence of the disease in the sample, the mistaken recording of the clinical conditions of the third molar teeth, and dichotomization of the data collected also contributed to the occurrence of the paradox "high agreement but low (sometimes negative) Kappa" [13, 14].

As regards the investigations about the most sensitive clinical criteria in view of the present profile of dental caries development, a classical study conducted by Nyvad et al. [15] showed that the *PA* values for detecting caries lesions ranged between 94.2 and 96.2%. The intra-examiner Kappa values ranged from 0.74 to 0.85, while the inter-examiner Kappa values ranged from 0.78 to 0.80. In this study, the sample was composed of 50 children, selected from among a group of 889 children in the age range from 9 to 14 years of age, under high prevalence of dental caries, examined by 2 examiners during a period of 3 years.

Braga et al. [16] evaluated in vitro reproducibility of Nyvad criteria [15] and "International Caries Detection and Assessment System II" (ICDAS-II) [17] for severity and activity of occlusal caries lesions in primary teeth. Two samples of extracted primary molars (sample 1, $n = 38$; sample 2 $n = 69$) were evaluated independently by two examiners. The intra-examiner Kappa values for caries detection were 0.89 and 0.90 (unweighted) and 0.96 and 0.98 (weighed) for Nyvad criteria and 0.90 and 0.93 (unweighted) and 0.91 and 0.98 (weighted) for ICDAS-II. The inter-examiner Kappa values were 0.86 and 0.93 (unweighted) and 0.96 and 0.99 (weighted) for Nyvad criteria and 0.86 and 0.97 (unweighted) and 0.82 and 0.97 (weighted) for ICDAS-II.

Investigative studies into the line of evaluation of caries detection methods showed that in general good performance does not refer to their precision.

Kockanat and Unal [18] investigated the in vivo and in vitro performance of traditional and novel tests (clinical examination under ICDAS-II, DIAGNOdent® pen, CarieScan PRO, and SoproLife camera) for caries detection on occlusal surfaces in primary teeth. One hundred twenty primary molar teeth past exfoliation time and with indication for extraction, from children aged between 9 and 12 years old, were selected for this study. The reproducibility results from its two examiners are presented in Table 32.3.

Assuring the correct indication of the measurement of reproducibility considering the nature of their data, Mortensen et al. [19] evaluated the performance of other methods for the detection of carious lesions (CarieScan PRO, ACIS, DIAGNOdent® pen, LF-pen, and bitewing radiographs) on the occlusal tooth surface in vivo, and measured the intra- and inter-examiner reproducibility of the categorical data (from clinical under ICDAS-II and bitewing radiographic examinations) by means of the weighted Kappa, while the numerical data (from ACIS and LF-pen) were analyzed by means of the intraclass correlation coefficient (ICC). The sample in this study consisted of 62 adults examined by 2 examiners. The weighted Kappa values were 0.81 to 0.91 for ICDAS and 0.90 to 0.92 for bitewing radiographs.

The detection of these incipient caries lesions in the tooth enamel surface, by means of conventional techniques and technologies, especially in epidemiological inquiries, has produced optimistic results at the expense of doubtful teeth recorded as being "healthy" [6]. The measurement of reproducibility from "tooth-to-tooth" (by groups of teeth, e.g., "molars") or by "dental sites" (e.g., occlusal surfaces of posterior teeth) is an interesting proposal [4], as opposed to the method of measuring the standard reproducibility, proposed in *Oral Health Surveys: Basic Methods* [6], for obtaining a trustworthy result.

Table 32.3 Reproducibility in Kockanat and Unal [18]

Diagnostic tests	Intra-examiner				Inter-examiner					
	Examiner 1		Examiner 2		In vivo		In vitro		In vitro *(2 weeks later)*	
	κ	ICC[a]	K	ICC	K	ICC	κ	ICC	κ	ICC
Visual inspection	0.99	0.99	0.96	0.98	0.94	0.99	0.98	0.99	0.98	0.99
Radiographic	–	–	–	–	0.85	0.88	–	–	–	–
DIAGNOdent® pen	0.94	0.98	0.91	0.98	0.95	0.99	0.95	0.97	0.95	0.99
CarieScan PRO	0.87	0.98	0.90	0.97	0.95	0.97	0.85	0.94	0.91	0.96
SoproLife camera	0.97	0.98	0.97	0.99	0.99	0.99	0.99	0.99	0.96	0.99

[a]*Intraclass correlation coefficient*

32.2.3 Intraclass Correlation Coefficient

The *intraclass correlation coefficient* (*ICC*) or *reliability coefficient* (*R*), originally proposed by Fisher [20], in 1954, is an instrument for measuring reproducibility used in studies of the test-retest type and also intra- and inter-examiner agreement for quantitative or numerical and continuous variables. Their most common indications include the evaluation of diagnostic tests in the clinical, laboratory, and epidemiological areas and of psychometric data collection instruments applied to more than one individual [7, 21–23]. The ICC simultaneously reflects the degree of correlation and agreement among the measurements made [2, 23], even when there are violations of normality of the distributions, which make it more robust [1].

In conceptual terms, the simpler expression of the ICC, from which all its other versions are derived, is presented as follows:

$$\mathrm{ICC} = \frac{\sigma_e^2}{\sigma_e^2 + \sigma_d^2}$$

where σ_e^2: variability among units
σ_d^2: intra-unit variability

or also by the formula:

$$\mathrm{ICC}(1,1) = \frac{\mathrm{BMS} - \mathrm{WMS}}{\mathrm{BMS} + (k-1)\,\mathrm{WMS}'}$$

where BMS: between-target mean square
WMS: within-target mean square
k: number of examiners

For the different applications of the ICC, different versions are required. These different versions of the ICC may generate widely differing results when applied in one and the same set of data. Herein lies the importance of researchers having in-depth knowledge about its different forms and applications to enable trustworthy results to be obtained in their studies. Selecting the version of the ICC suited to the purposes of their studies will depend on the answers to the questions proposed by Shrout and Fleiss [21], McGraw and Wong [22], Koo and Li [23], and Miot [1], listed as follows:

(a) Do we have the same set of examiners for all subjects?
(b) Do we have a sample of examiners randomly selected from a larger population or a specific sample of raters?
(c) Are we interested in the reliability of a single examiner or the mean value of multiple examiners?
(d) Is a one-way or two-way analysis of variance (ANOVA) appropriate for the analysis of the reliability study?
(e) Are differences between the examiners' mean ratings relevant to the reliability of interest?
(f) Is the unit of analysis an individual rating or the mean of several ratings?
(g) Do we concern about consistency or agreement?

The ICC can be calculated manually by means of a ratio of variances, both by classical methods (e.g., the restricted maximum likelihood (REML) method), by the Bayesian methods (e.g., integrated nested Laplace approximations (INLA) or Markov chain Monte Carlo (MCMC)), and by means of statistical programs such as the "Statistical Analysis System" (SAS®) or "IBM's Statistical Package for the Social Sciences" (SPSS®). Its values vary from "0" (non-reproducible diagnostic test) to "1" (highly reproducible diagnostic test) [7]. In spite of being arbitrary, a suggestion for interpreting its values is presented as follows:

ICC values	Strength of agreement
ICC < 0.4	Poor
0.4 ≤ ICC < 0.75	Satisfactory
ICC ≥ 0.75	Excellent

Considering that the reproducibility values of diagnostic tests obtained by means of the weighted Kappa are the same as those obtained by the ICC, Miot [1] suggested that its interpretation should be the same as that of the Kappa statistic. In this sense, Koo and Li [23] presented another interpretation of the ICC:

ICC values	Strength of agreement
ICC < 0.5	Poor
0.5 ≤ ICC < 0.75	Moderate
0.75 ≤ ICC < 0.9	Good
ICC > 0.9	Excellent

With a view of having an even more secure interpretation of the ICC, Silva et al. [2] suggested simultaneously performing the ICC with other statistical tests such as the paired-*t* test, Cronbach's alpha coefficient, and Bland-Altman plots [23, 24] in studies on the reproducibility of diagnostic tests.

Singh et al. [25] evaluated the clinical performance of ICDAS-II, radiovisiography (RVG), and CarieScan PRO in the detection and evaluation of carious lesions on the occlusal surfaces of primary molars. The reproducibility, measured by the ICC is presented in Table 32.4, as follows:

Table 32.4 ICC values from Singh et al. [25]

Diagnostic tests	In vivo intra-examiner reliability			In vitro inter-examiner reliability		
	ICC	95% CI	*p*-value	ICC	95% CI	*p*-value
ICDAS II	0.92	0.91 (0.78–0.98)	0.0001	0.93	0.92 (0.72–0.99)	0.0001
RVG	0.86	0.93 (0.86–0.97)		0.89	0.90 (0.81–0.96)	
CarieScan PRO	0.93	0.90 (0.88–0.99)		0.91	0.90 (0.87–0.98)	

In this study, there were 20 carious primary teeth, close to the time of exfoliation, from children 8 to 11 years of age who were included in the study. The interval between the evaluations of these teeth, to calculate the intra-examiner reliability, was 1 week [25].

The ICC (numerical data) was used alongside Kappa statistics (categorical data) in Kockanat and Unal [18] and Mortensen et al. [19] to determinate the reproducibility of tests for dental caries detection. The ICC values from Kockanat and Unal [18] are presented in Table 32.2. In Mortensen et al. [19], the ICC values ranged between 0.65 and 0.88 for CarieScan PRO and 0.89 and 0.94 for DIAGNOdent® pen. However, the WHO recommendation [6] is that the Kappa statistic should be adopted in dental caries studies that adopt the DMFT index.

Yuen and Nelson [26] assessing the test-retest reliability of the Oral Health Impact Profile (versions OHIP-49 and OHIP-14) in 3-month intervals among 39 adults with systemic sclerosis found the results presented in Table 32.5:

Table 32.5 ICC values from Yuen and Nelson [26]

OHIP version	Time	ICC (95% CI)
OHIP-49	Baseline–3 months	0.84 (0.66–0.92)
	3–6 months	0.69 (0.48–0.82)
OHIP-14	Baseline–3 months	0.82 (0.65–0.91)
	3–6 months	0.61 (0.37–0.78)

Machado et al. [27], comparing the performance of partial-mouth periodontal examination (different cutoff points of PMPE protocols) with the full-mouth examination (FME) in the assessment of the prevalence and extent of gingival bleeding, in a sample of 1134 12-year-old adolescents, found PMPE ICC values higher than the FME (ICC $\geq$ 0.81), except for the random half-mouth protocol.

The systematic review of Zaki et al. [28] showed that the ICC is the most used method to assess the reliability of diagnostic tests or instruments measuring continuous outcomes. However, the authors warn that many studies do not report which version of the ICC is used. This information is important to check the correctness between the ICC indication and the data in each study.

32.2.4 Dice Index

The *Dice index* (*Sørensen-Dice index, Dice's coefficient, Dice similarity coefficient*) is a measurement of similarity among sets (set = each evaluation of a subject by an examiner) which is sometimes presented as an alternative way of measuring the reproducibility of diagnostic tests. Extremely easy to calculate (easily calculated manually), the Dice index (D) is indicated in situations in which only one class is constituted as the object of interest; that is, only the record presence/absence of a disease under study is important in the sample [2, 29]. Its main limitation resides precisely in its ease of calculation; that is, the fact that only the results of agreement and disagreement among examiners is considered in relation to the true-positive cases (class of interest) restricts its use in epidemiological studies [2].

For better understanding of its formula, we have taken a 2×2 contingency table (Table 32.6) as example:

Dice index formula

$$D = \frac{(2a)}{(2a+b+c)}$$

The closer to the value "+1," the greater the similarity measured by the Dice index, among the sets under study, consequently, the greater the reproducibility of the diagnostic test.

An example of its use in dental research directed toward dental caries is presented in the study of Assaf et al. [30]. In the cited study, the authors compared three measurements of reproducibility for calibration in epidemiological inquiries into dental caries. A total of 11 dentists, previously trained and calibrated in accordance with the diagnostic criteria of the World Health Organization, together with the inclusion of initial carious lesions in enamel (WHO+IL), examined

Table 32.6 2×2 contingency table

Examiner #1		Examiner #2	
		Dental condition	
		Decayed	Sound
Dental condition	Decayed	A	B
	Sound	C	D

Table 32.7 Reproducibility measurements in Assaf et al. [30]

Reproducibility measurements	WHO diagnostic criteria	WHO+IL diagnostic criteria
Kappa statistics	0.95 (95% CI: 0.93–0.98)	0.90 (95% CI: 0.86–0.93)
Dice index	0.93 (95% CI: 0.89–0.98)	0.69 (95% CI: 0.54–0.77)
Percentage of agreement	0.96 (95% CI: 0.95–0.99)	0.93 (95% CI: 0.90–0.95)

23 schoolchildren in the age range from 6 to 7 years of age. The results of this study are presented in Table 32.7 as follows:

Considering the WHO diagnostic criteria being less complex than those of the WHO+IL, three of the reproducibility measurements were observed to contain some similarity [30].

32.3 Validity of Diagnostic Tests

Diagnosis is the determination of a disease from its signs and symptoms. This differs from the detection of signs and symptoms themselves. In practical clinical work, the diagnosis translates into evaluation of the disease activity and constitutes the basis for making treatment decisions. The diagnosis portrays a momentary situation. This portrayal is made based on the clinical judgment of experienced professionals, either supplemented (or not) by diagnostic tests for diagnosing specific diseases or conditions, such as dental caries [31, 32].

Adjunct diagnostic tests for the diagnosis and/or detection of oral diseases are desirable when these are not easily detected by traditional tests. A classic example in Dentistry is the detection of dental caries in recent decades. Nowadays, the detection of incipient carious lesions on enamel surfaces requires more sensitive tests. The development of new diagnostic tests comprises the evaluation of their reproducibility and validity [31].

In diagnostic test validity studies, with categorical data producing dichotomous outcomes (e.g., "healthy" and "diseased"), the involvement of a previously defined "gold standard" is imperative [7]. The term "gold standard" refers to the most exact diagnostic method (free of errors) for each disease studied under a specific setting [33].

In Dentistry, many methods can be adopted as a "gold standard," for example, histological validation for dental caries at enamel microscopic level (in vitro studies; laboratorial settings); drilling dental surfaces for hidden caries lesions (in vivo studies; clinical settings); biopsies and exploratory surgeries for oral cancer lesions (in vivo studies; clinical settings); and clinical examination complemented (or not) by bitewing radiographs, for example, of occlusal surfaces of posterior teeth or periodontal disease diagnosed by an experienced examiner (in vivo studies; epidemiological settings). When selecting a gold standard, the opportunity, ethical issues, and biohazard damage to the researcher for the work must be seriously considered. To sum up, the gold standard gives the "true" value (if the subject is "healthy" or "diseased") of a diagnostic test [7, 31, 33, 34]. Fyffe et al. [34] and Rutjes et al. [35] showed evidence that when it is impossible to use an established method as the gold standard, the majority of the methods identified in the scientific literature try to construct a reference standard that makes it possible to perform measurements of validity, notably sensitivity and specificity, which produce trustworthy results. Moreover, according to Rutjes et al. [35], some methods are promising, such as the construction of a reference standard using consensus panel methods and validation of tests out with the accuracy paradigm; however, these require further methodological researches.

The validity measures are calculated from the examination outcomes (dichotomous outcomes from categorical data) between the gold standard method and the ordinary test registered in a 2×2 contingency table as follow:

- *Efficiency* (*Se*): a/(a + c)
- *Specificity* (*Sp*): d/(b + d)
- *Prevalence of real diseased*: (a + c)/N
- *Estimated prevalence* (*diagnostic test*): (a + b)/N
- *Prevalence of disease for test-positive patients*: a/(a + b)
- *Prevalence of disease for test-negative patients*: c/(c + d)
- *Positive predictive value* (*PPV*): a/(a + b)
- *Negative predictive value* (*NPV*): d/(c + d)
- *Likelihood ratio of positive test result* (*LR+*): a/(a + c):b/(b + d)
- *Likelihood ratio of negative test result* (*LR-*): c/(a + c):d/(b + d)
- *False-positive rate* (*FPR*): 1 – Sp
- *False-negative rate* (*FNR*): 1 – Se

Table 32.8 Contingency table for validity evaluation

		Disease (gold standard)		
Diagnostic test (examiner)		Present	Absent	
	+	True-positive (a)	False-positive (b)	a + b
	–	(c) False-negative	(d) True-negative	c + d
		a + c	b + d	N

- *Correct classification* (*accuracy*, *effectiveness*, *crude hit rate*, *proportion correctly classified*): (a + d)/N
- *Incorrect classification*: (b + c)/N
- *Youden's J statistic* (*J*): (Se + Sp) – 1
- *Diagnostic odds ratio* (*DOR*): (a/c)/(b/d)
- *Efficiency* (*Ef*): (PPV + NPV)/2

When dealing with continuous quantitative data, the researcher must define a cutoff point to differentiate "healthy" from "diseased" cases and then proceed with the validity evaluation of the diagnostic test.

Validity measures for a diagnostic test can be performed by statistical computing (e.g., "Statistical Analysis System" (SAS®) or "IBM's Statistical Package for the Social Sciences" (SPSS®)) or manually because they are easy, as seen in Table 32.8. Calculation and presentation of the confidence interval (95% CI) along with the validity measures results give the validity study of diagnostic tests more robustness.

32.3.1 Sensitivity and Specificity

The concepts of *sensitivity* and *specificity* of a diagnostic test were introduced by Yerushalmy [36], in 1947, in diagnostic scientific literature. These traditional validity measures are used when the definitions of exposure and outcome variables are categorical. *Sensitivity* (*true-positive probability*; *true-positive rate*) is defined as the proportion of true-positives that are correctly identified by the diagnostic test. *Specificity* (*true-negative probability*; *true-negative rate*) is defined as the proportion of true-negatives that are correctly identified by the diagnostic test [37]. Both measures are often regarded as the benchmarks of test performance of diagnostic tests. However, researches must be mindful when generalizing their results. *Sensitivity* and *specificity* vary with clinical characteristics. This fact, added to disease prevalence and characteristics (such as age, gender, and exposition to risk factors) of the sample tested, selection, and other methodological biases, must also be considered in the analysis of a diagnostic test performance. So, comparing *sensitivity* and *specificity* values among different populations, even when Se ≥ 70% and Sp ≥ 90%, deserves some caution [7, 37–39].

32.3.2 Predictive Values

The positive predictive value (*PPV*) is the proportion of subjects who really have the disease, among all the subjects diagnosed as being "positive" by the diagnostic test. The *negative predictive value* (*NPV*) is the proportion of subjects who are really healthy among all the subjects diagnosed as being "negative" by the diagnostic test [40]. *Sensitivity* and *negative predictive values* are directly proportional; that is, a high *sensitivity* value of a diagnostic test corresponds to a high *negative predictive value*. This is due to the reduction in frequency of false-negative results, showing a higher probability that a subject diagnosed as being "negative" does not present the disease. Whereas, an elevated *specificity* value of a diagnostic test will correspond to an elevated *positive predictive value* resulting from the reduction in the frequency of false-positive results, showing a higher probability that a subject diagnosed as being "positive" has or will develop the disease. To sum up, the importance of the prevalence of disease in the study sample must not be overlooked and must be representative of the population from which it originates [38, 39, 41].

According to Henderson [33], the predictive values have been deprecated by the scientific community, in favor of other measurements such as *likelihood ratios* or *ROC curves,* as a result of dependence on the prevalence of the disease in the population.

This being so, elevated positive predictive values are desirable when a therapy is being recommended in which the biological and/or financial costs exceed its benefits to the individual diagnosed as being ill [42].

32.3.3 Likelihood Ratios

The *likelihood ratios* indicate the value of the diagnostic test for increasing assurance in positive diagnosis. A higher value denotes a diagnostic test useful, not necessarily that such test, if positive, is a good indicator of the prevalence disease. This measure of validity avails all information of a diagnostic test: summarizes its sensitivity, specificity and accuracy information; and calculates the disease probability after a positive or negative test result. Because of this, in some circumstances, *likelihood ratios* are preferable instead *sensitivity*, *specificity*, and even *ROC curve* [40]. As other measures of validity, *likelihood ratios* are also influenced by the disease prevalence considering dichotomous results of the diagnostic tests [38].

The *likelihood ratio of positive test result* (*LR*+) is the probability that a subject diagnosed as being ill is really ill (true-positive) instead of being false-positive, while the *likelihood ratio of negative test result* (*LR*-) is the probability that a subject diagnosed as being healthy (true-negative) is truly healthy instead of being false-negative. Therefore, the better the performance of a diagnostic test, the higher will be the *LR*+ value, and the lower will be the *LR*- value [39].

However, according Zweig and Campbell [43], *likelihood ratios* are not good tools for assessing or comparing test performance, because they calculate the post-test probability of disease. *Likelihood ratios* only make it possible to review the pre-test probability of disease, which is calculated by using the Bayes theorem, for example.

32.3.4 False-Positive Rate (FPR) and False-Negative Rate (FNR)

The *FPR* of a diagnostic test is the proportion of subjects erroneously considered ill, when in reality, they are healthy, while its *FNR* is the proportion of subjects erroneously considered healthy, when in reality, they are ill. Both rates express information complementary to the sensitivity and specificity of a diagnostic test, because they reveal the proportion of individuals erroneously classified for the two conditions. Taking the risk of dental caries, for example, *FPR* is the proportion of subjects supposedly at high risk among those whose actual caries increment during a follow-up was low, while *FNR* is the proportion of subjects diagnosed at low risk among those whose actual caries increment was high [42].

32.3.5 Correct Classification

This global measure (also called *accuracy*, *effectiveness*, *crude hit rate*, *proportion correctly classified*) summarizes the information about a diagnostic test validity, notably in relation to its true results (subjects correctly classified as positive/diseased or negative/sound), into a single numerical value facilitating its understanding [40, 42]. So *accuracy* is the ability of a diagnostic test to differentiate between the patient and healthy cases correctly. It is calculated by dividing the sum of correct classifications (the diagonal line formed between "real diseased" and "real healthy" individuals from contingency tables) by the total number of individuals examined. This measure is affected by the prevalence of the disease and is best applied in populations with low prevalence of the disease. Under the same *sensitivity* and *specificity*, diagnostic accuracy of a diagnostic test increases as the disease prevalence decreases. *Predictive values* should always be presented in conjunction with the *accuracy* [44].

32.3.6 Youden's J Statistic

The *Youden's J statistic* or *Youden index* [45] is another way to summarize a validity of a diagnostic test into a single numerical value. It is a global measure of a test performance, used to evaluate the discriminative power of a diagnostic test. *Youden's J statistic* enables comparison among different diagnostic tests. However, for comparison among different tests, the other validity measurements must also be consulted, because studies with different sensitivity and specificity values may generate the same value as that of *Youden's J statistic.* Šimundić [44], when illustrating this situation, demonstrated that a test with Se = 0.9 and Sp = 0.4 and another with Se = 0.6 and Sp = 0.7 presented the same J = 0.3.

In an ideal diagnostic test, in which the false-positive and false-negative rates are equal to 0, *Youden's J statistic* assumes its maximum value equal to "1." However, when this test present equal sensitivity and specificity values, *Youden's J statistic* assumes value "0." Therefore, according to this index, the option to take should be a diagnostic test that presents the lowest sum of the proportions of classification errors [7, 42].

The prevalence of disease does not affect *Youden's J statistic*, but the spectrum of the disease does [44]. *Youden's J statistic* can be understood as the summary measure of the ROC curve in validity studies, which defined the maximum potential effectiveness of a diagnostic test. *Youden's index* and *ROC curve* (as will be seen below) measures the effectiveness of a diagnostic test and enables the selection of an optimal threshold value (cutoff point) for the test [46, 47].

In Fluss et al. [46], the estimation of *Youden's index* and its associated cutoff point was performed by diagnostic test data distribution methods based on: (1) normal assumptions, (2) transformations to normality, (3) empirical distribution function, and (4) kernel smoothing. The kernel method seems to be the best choice to estimation *Youden's index* and its optimal threshold. According to the authors, the confidence intervals must be considered in studies of this nature [46].

32.3.7 Diagnostic Odds Ratio

Diagnostic odds ratio (*DOR*) is another global measure for diagnostic accuracy, used for general estimation of discriminative power of diagnostic procedures and also for the comparison of diagnostic accuracies between two or more diagnostic tests. It is the ratio of the odds of positivity (positive diagnostic results) in subjects with disease relative to the odds in healthy subjects. Thus, *sensitivity* and *specificity* values influence *DOR* values [44].

32.3.8 Receiver Operating Characteristic Curve

Originally designed to detect electronic signals and problems with radar in the early 1950s, the global and graphic statistical tool *receiver operating characteristic curve* (*relative operating characteristic curve*; *ROC curve*) was found useful in researches in the medical area in the late 1960s [39]. This new application was owing to the fact that the *ROC curve* quantitatively described the performance of a diagnostic test, whose result could be treated as a continuous variable or categorical ordinal [48].

Graphic representation of the *ROC curve* consists of plotting the *sensitivity* (*Se*) values on the axis of the ordinals (Y axis), against the false-positive rate values (*FPR* = 1 – Sp) on the axis-of-abscissas (X axis) facilitating visualization and determination of the best cutoff point, where the discriminatory power of the test is higher, that is, where the capacity of the diagnostic test to discriminate between healthy and sick subjects is greater [39]. Each point on the *ROC curve* represents a sensitivity/specificity pair corresponding to a particular decision threshold. This graphic representation makes it possible to compare various diagnostic tests simultaneously in one and the same graph, and this is the greatest advantage of this validity measurement [43, 49].

Other advantages of the *ROC curve* include [43]:

1. Comprehensive representation of pure *accuracy*.
2. It does not require selection of a particular decision threshold. It represents the whole spectrum of possible decision thresholds.
3. It is independent of disease prevalence.
4. No care need be taken to obtain samples with representative prevalence.
5. It requires no grouping or binning of data.
6. *Sensitivity* and *specificity* are readily accessible.

Among its apparent disadvantages, Zweig and Campbell [43] pointed out the following:

1. Actual decision thresholds are usually not displayed in the plot (though they are known and used to generate the graph).
2. The number of subjects is also not shown on the display (although it is in the dot diagram), and as the sample sizes decreases, the ROC plots tend to become increasingly jagged and bumpy.
3. The generation of plots and calculation of parameters is cumbersome without computer software.

The *area under curve* (*A*, A_Z, *AUC*, *or W*) is calculated from the area formed under the *ROC curve* and the abscissa axis. The higher the value of the area under the *ROC curve*, that is, the closer the curve comes to the axis of ordinals (Y axis), the better will be the validity of the diagnostic test [49]. The *AUC* is equivalent to the value of the Mann-Whitney U test and also to the probability of correctly ranking a (normal, abnormal) pair (i.e., non-diseased-diseased individuals) (Henderson, 1993). Diagnostic tests presenting *AUC* values ≤0.5 (50%) must be discarded, because they may detect disease in research subject merely by chance [42].

In spite of the classification of AUC values being arbitrary, a proposal for interpreting these values is presented as follows [44]:

AUC values	Diagnostic accuracy
0.9–1.0	Excellent
0.8–0.9	Very good
0.7–0.8	Good
0.6–0.7	Sufficient
0.5–0.6	Bad
<0.5	Test not useful

Taking the diagnostic methods for dental caries on occlusal surfaces as an example, exclusive examination with DIAGNOdent® (DD), visual inspection complemented with the radiographic bitewing exam (VI2 + BW), and visual inspection complemented with DIAGNOdent® and radiographic bitewing exams (VI2 + DD + BW), evaluated in the study of da Silva et al. [50], and applying the ROC curve and area under curve, it was verified that the results of the cited study were corroborated (Table 32.9, Fig. 32.1).

Thus, along general lines, we find that an "ideal" diagnostic test (under ideal conditions of use, hypothetically) is that which present the following values relative to its validity: *Se* and *Sp* values of 100%; *FPR* and *FNR* equal to 0%; *PPV* and *NPV* of a 100%; *J* = 1; and *AUC* = 1 (100%). However, for epidemiological studies, *Se* and *Sp* ≥ 80% and *J* = 0.6 are acceptable [42, 51]. A useful medical test (under "real" condition of use) must present its validity values as closely as possible to the values presented previously.

32.3.8.1 Tendencies in Studies About the Reproducibility of Tests for Dental Caries Detection

The dynamic and reversible nature of dental caries (in its pre-cavitation stage) has driven the research of new tests and methodologies for the early detection of

Table 32.9 ROC curve and AUC for diagnostic methods from da Silva et al. [50]

Results	DD (curve A)	VI2 + BW (curve B)	VI2 + DD + BW (curve C)
Decayed teeth	682	983	1109
Sound teeth	1368	1249	1078
Cutoff point	(0.14; 0.57)	(0.08; 0.88)	(0.19; 0.92)
Distance (d)	0.45	0.15	0.21
Area under curve	0.7141	0.8964	0.8634
Sensibility and specificity	0.57; 0.86	0.88; 0.92	0.92; 0.81
Positive and negative predictive value	0.76; 0.81	0.89; 0.91	0.79; 0.93
Accuracy	0.73	0.90	0.86
Standard error	0.0126	0.0072	0.0079
95% CI (area)	0.6894–0.7387	0.8823–0.9104	0.8479–0.8788

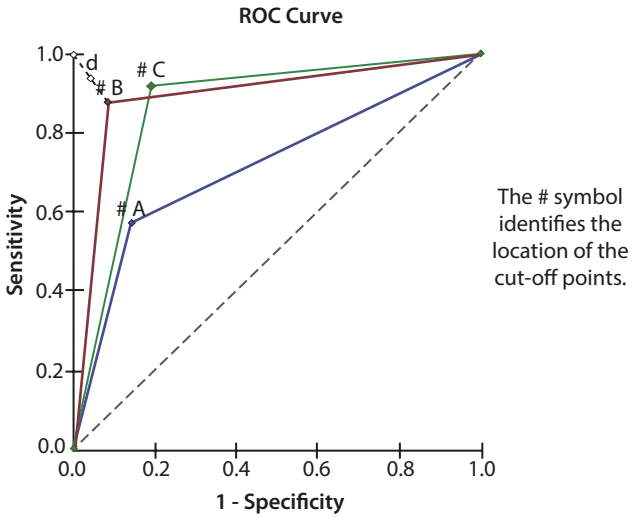


Fig. 32.1 ROC curves for diagnostic methods from da Silva et al. [50]

lesions, notably on the occlusal surface of posterior teeth, all over the world [52]. As a result of this fact, a large portion of present-day studies about the validity of diagnostic tests in Dentistry have brought this topic into laboratory, clinical, and epidemiological scenarios. In a systematic review of the literature conducted by Twetman et al. [53], with the aim of evaluating the accuracy of test for the detection of caries lesions (fiberoptic, fluorescence, and electrical tests), in the detection and quantification of dental cares, measurements of validity, *sensitivity*, *specificity*, *predictive values* (*positive* and *negative*), *accuracy*, Youden's *index*, and *ROC curve*/*AUC*, among others, have been used in original studies selected in accordance with the inclusion criteria pre-established by the authors. A summary of validity measures in this systematic revision is presented below:

Twetman et al. [53] concluded that in spite of the limited quality of the scientific evidence (Table 32.10), the mean values of *sensitivity* (70%) and *specificity* (80%) for ECM and DIAGNOdent®, for incipient lesions in enamel and cavities in dentin, enable these adjunct tests for the detection of dental caries lesions. Furthermore, the authors drew attention to the need for standardization of in vitro and in vivo study designs, with a view to the interpretation and adoption of these tests by professionals.

Sensitivity, *specificity, positive and negative likelihood ratios*, and *diagnostic odds ratio* values from the 54 studies included in the Ekstrand et al. (2018) systematic review about the ICDAS for assessing coronal caries were statistically pooled. The *receiver operating characteristic curves* (ROC curve) were used to summarize these results. The Cochran Q and I^2 tests were used to evaluate the heterogeneity among the included studies [54].

Ekstrand et al. [54] showed evidence that ICDAS presented a substantial level of reproducibility and accuracy for assessing primary coronal caries lesions. The scarce amount of literature concerning the ICDAS and secondary and root caries justify this conclusion. Thus, the ICDAS robustness encourages its use in clinical practice.

Information about costs and benefits could also be directly tied to the different cutoff points of a diagnostic test analyzed by means of the *ROC curve*, thus favoring the selection of its best cost-benefit ratio [55].

32.3.9 Bayes' Theorem

In epidemiology, Bayes' theorem is often used to obtain the probability of disease in a group of subjects with some characteristic on the basis of the overall rate of that disease (the prior probability of disease) and of the likelihoods of that characteristic in healthy and diseased individuals (Porta, 2014). The formula of Bayes' theorem is

$$P(D|S) = \frac{P(S|D)P(D)}{P(S|D)P(D) + P(S|\bar{D})P(\bar{D})}$$

Table 32.10 Summary of validity measures in Twetman et al. [53]

Diagnostic test	No. of studies	Sensitivity mean (SD)[a]	Specificity mean (SD)[a]	Youden's index	Grade of evidence
Fiberoptics *FOTI, Di-FOTI*	4	0.44 (0.33)	0.74 (0.40)	0.18	●○○○
Laser fluorescence					
LF enamel level	9	0.66 (0.29)	0.77 (0.19)	0.43	●●○○
LF dentine level	14	0.72 (0.20)	0.82 (0.16)	0.54	●●○○
Electrical caries monitor *ECM dentine level*	4	0.73 (0.14)	0.79 (0.11)	0.52	●●○○

Source: adapted from Twetman et al. [53]
[a]Standard deviation

where D = disease
S = symptom
$\bar{D}$ = no disease
$P(D)$ is the overall probability of disease (also called the crude, unconditional, or prior probability)
$P(S|D)$ is the probability of the symptom given the disease
$P(S|\bar{D})$ is the probability of the symptom given no disease
$P(D|S)$ is the probability of disease given the symptom (also called the conditional or posterior probability).

The theorem is sometimes presented in terms of the odds of disease before knowing the symptom (prior odds) and after knowing the symptom (posterior odds). The Bayesian standpoint supports the use of subjective probabilities as a degree of belief, the use of Bayes' theorem to modify prior probabilities by *likelihood ratios* to obtain posterior probabilities, and a consideration of the consequences of incorrect decisions [39, 43].

The Bayes' theorem may be also used with a diagnostic test, or a sequence of diagnostic tests (previous knowledge of *sensitivity* and *specificity* values), to calculate the probability that a subject may have a particular diagnosis given the appearance of some symptoms or test result [33, 39]. The Bayes' theorem can also be used to assess the impact of diagnostic information on the opinion of raters in a study of the efficacy of diagnostic procedures and together with the *likelihood ratio* and *ROC curve* to measure the diagnostic power of the diagnostic test at any selected decision threshold [33].

In the study of Neuhaus et al. [56], the performance in caries detection of the clinical visual exam under ICDAS-II, radiography, laser fluorescence (LFPen), and LED fluorescence have been calculated by means of Bayesian analyses. In the cited study, the best diagnostic performance was obtained by a combination of the visual clinical exam, under ICDAS-II, complemented by the radiographic exam (post-test probability of 0.73) at the dentin threshold.

Although the Bayesian estimates presented accuracy and precision values similar to estimates based on likelihood, they have computational advantages and make it possible to express all the forms of uncertainties in terms of probability, in the modeling of the dmft/DMFT index [57]. Matranga et al. [57] also showed evidence that the use of previous information about the parameters of the DMFT index in Bayesian modeling is desirable, notably in observational studies in which sampling is not randomized and there is no strict control of biases.

Detailing of the design and how reproducibility and validity studies are conducted must also be available to their readers, making it possible for them to judge the trustworthiness and applicability of the study findings [58]. Therefore, the adoption of guidelines, such as "Guidelines for Reporting Reliability and Agreement Studies (GRRAS)" [59] or "Standards for Reports of Diagnostic Accuracy (STARD)" [60], for example, must also be encouraged in Dentistry.

The concern expressed by the World Health Organization with regard to the selection and implementation of in vitro diagnostic tests in communities around the world, notably those situated in localities whose resources are limited, culminated in the publication of a guide to aid professionals in the selection of these tests. Thus, ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users), originally designed for diagnostic tests for sexually transmitted infections (STIs), by the WHO itself [61], in conjunction with the six steps proposed by *Médecins Sans Frontières*, for the selection and implementation of in vitro *diagnostic tests*,

has been proposed for this purpose in the field of health in general [62]. In Dentistry, the value of these methods with a view to improving the quality of specific scientific literature will be our challenge from now on.

32.4 Final Considerations

The results of studies on the reproducibility of diagnostic tests in a sample representative of the population, no matter how well planned and executed their sessions of training and calibration of examiners are, must not be compared with the results of other studies. Each sample in these studies reflects the epidemiological profile of the local population where these studies were conducted [7], and it is therefore impossible to assure the comparability between samples in these studies. Whenever possible, the results of these studies must be presented with their respective intervals of confidence and level of significance adopted. A high Kappa or ICC value with a very ample CI of 95% could generate uncertainty about its credibility [63].

Relative to the validity of diagnostic tests, the use and concomitant presentation of their different measurements in a single study must be encouraged, thereby providing a complete panorama of the performance of the tests evaluated [43, 44]. According to Whiting et al. [64], the main effects of biases and variations in diagnostic validity studies impact on demographic features, disease prevalence and severity, partial verification bias, clinical review bias, and observer and instrument variation. A distorted selection of participants, absent or inappropriate reference standard, differential verification bias, and review bias also impact – to some degree – on the results of a diagnostic test validity study [64]. Therefore, even in a diagnostic test validity study, the representativeness of the target population from which the main sample is extracted must be sought, with a view to obtaining trustworthy results [38, 43, 54]. Thus, when evaluating the performance of diagnostic tests in different populations, the ideal would be replication of the original study in the samples of the different target populations in whom the researchers intend conducting the study in a manner similar to that adopted in studies of translation and validation of questionnaires into languages differing from their original language.

Other items of care taken in planning studies about the performance of diagnostic tests go beyond standardization of the methods of measurement, examiner training and calibration, for example, blinding or masking of examiners, optimization, automation, and calibration of equipment used as the main or auxiliary instruments of diagnosis, also compete for adequate and trustworthy reproducibility and validity values. The internal (detection of potential biases) and external validity (evaluating the potential generalization and applicability of the results) of a study on the performance of a diagnostic test are important to the decision of a researcher to replicate it in the future and to professionals adopting it in their clinical practice [60]. Parameters such as the feasibility of diagnostic tests (financial costs to the health system and/or individuals, feasibility, opportunity, simplicity, facility of performing the test) and its impact on clinical decisions and outcomes in health (particularly its harmlessness to the researcher/professional and individual and minimization of iatrogenic damage) must also be thought of in studies about performing these tests [43, 65].

32.4.1 Outlook

With changing in development profile of oral diseases along the years, especially dental caries, new diagnostic tests are required. So, to adopt or to refute such diagnostic tests, reproducibility and validity studies well designed and conducted are quite essentials. The importance to know how and when to use a specific method to calculate reproducibility or validity of diagnostic tests is growing.

32.4.2 Closing Remark

Standardization of methods used in researches, examiners training, calibration, blinding, or masking, as well optimization, automation and calibration of equipment used as the main or auxiliary instruments of diagnosis, contribute for adequate and trustworthy reproducibility and validity results.

There are several methods to calculate reproducibility and validity of diagnostic tests. The knowledge of how they work and when each one is indicated is crucial to design and perform a study about new diagnostic tests. Whenever possible reproducibility and validity must be present concomitantly to provide a complete panorama of the performance of the diagnostics tests evaluated [43, 44].

The comparison among validity studies can be done with caution, while such comparison among reproducibility studies must be avoided. The prevalence of the disease in the studied sample can compromise the reproducibility and validity results. The presentation of intervals of confidence and level of significance in such studies increases its credibility [63].

References

1. Miot HA. Agreement analysis in clinical and experimental trials. J Vasc Bras. 2016;15(2):89–92.
2. Silva AF, Velo MMAC, Pereira AC. Importância da reprodutibilidade dos métodos para diagnóstico em odontologia. RFO. 2016;21(1):115–20.
3. Lussi A, Hibst R, Paulus R. DIAGNOdent: an optical method for caries detection. J Dent Res. 2004;83(Spec Iss C):C80–3.
4. Assaf AV, Tagliaferro EPS, Meneghim MC, Tengan C, Pereira AC, Ambrosano GMB, Mialhe FL. A new approach for interexaminer reliability data analysis of dental caries calibration. J Appl Oral Sci. 2007;15:480–5.
5. da Silva RP, Assaf AV, Pereira SM, Ambrosano GM, Mialhe FL, Pereira AC. Reproducibility of adjunct techniques for diagnosis of dental caries in an epidemiological situation. Oral Health Prev Dent. 2011;9(3):251–9.
6. World Health Organization (WHO). Oral health surveys: basic methods. 5th ed. Geneva: WHO Press; 2013. 125 p. ISBN: 978-92-4-154864-9.
7. Szklo M, Javier Nieto F. Epidemiology: beyond the basics. 3rd ed. Burlington: Jones & Barlett Learning; 2014. 515 p. ISBN: 978-14-4-960469-1.
8. Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Measur. 1960;20(1):37–46.
9. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159–74.
10. Gwet KL. Handbook of inter-rater reliability. 4th ed. Gaithersburg: Advanced Analytics, LLC; 2014. 426 p.
11. Altman DG. Practical statistics for diagnostic students. London: Chapman and Hall; 1991.
12. Tonello AS, Silva RP, Assaf AV, Ambrosano GMB, Peres SHCS, Pereira AC, Meneghim MC. Interexaminer agreement dental caries epidemiological surveys: the importance of disease prevalence in the sample. Rev Bras Epidemiol. 2016;19(2):272–9.
13. Feinstein AR, Cicchetti DV. High agreement but low Kappa: I. The problems of two paradoxes. J Clin Epidemiol. 1990;43(6):543–9.
14. Cicchetti DV, Feinstein AR. High agreement but low Kappa: II. Resolving the paradoxes. J Clin Epidemiol. 1990;43(6):551–8.
15. Nyvad B, Machiulskiene V, Baelum V. Reliability of a new caries diagnostic system differentiating between active and inactive caries lesions. Caries Res. 1999;33:252–60.
16. Braga MM, Mendes FM, Martignon S, DNJ R, Ekstrand KR. In vitro comparison of Nyvad's system and ICDAS-II with lesion activity assessment for evaluation of severity and activity of occlusal caries lesions in primary teeth. Caries Res. 2009;43:405–12.
17. Ismail AI, Sohn W, Tellez M, Amaya A, Sen A, Hasson H, Pitts NB. The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. Community Dent Oral Epidemiol. 2007;35:170–8.
18. Kockanat A, Unal M. In vivo and in vitro comparison of ICDAS II, DIAGNOdent pen, CarieScan PRO and SoproLife camera for occlusal caries detection in primary molar teeth. Eur J Paediatr Dent. 2017;18(2):99–104.
19. Mortensen D, Hessing-Olsen I, Ekstrand KR, Twetman S. In-vivo performance of impedance spectroscopy, laser fluorescence, and bitewing radiographs for occlusal caries detection. Quintessence Int. 2018;49(4):293–9.
20. Fisher RA. Statistical methods for research workers. Edinburgh: Oliver and Boyd; 1954.
21. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420–8.
22. McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. Forming inferences about some intraclass correlation coefficients. Psychol Methods. 1996;1(1):30–46.
23. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016;15(2):155–63.
24. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307–10.
25. Singh R, Tandon S, Rathore M, Tewari N, Singh N, Shitoot AP. Clinical performance of ICDAS II, radiovisiography, and alternating current impedance spectroscopy device for the detection and assessment of occlusal caries in primary molars. J Indian Soc Pedod Prev Dent. 2016;34(2):152–8.
26. Yuen HK, Nelson SL. Test-retest reliability of Oral Health Impact Profile (OHIP-49) in adults with systemic sclerosis. Spec Care Dentist. 2014;34(1):27–33.
27. Machado ME, Tomazoni F, Casarin M, Ardenghi TM, Zanatta FB. Partial-mouth periodontal examination protocols for the determination of the prevalence and extent of gingival bleeding in adolescents. Community Dent Oral Epidemiol. 2017;45:427–33.
28. Zaki R, Bulgiba A, Nordin N, Ismail NA. A systematic review of statistical methods used to test for reliability of diagnostic instruments measuring continuous variables. Iran J Basic Med Sci. 2013;16(6):803–7.
29. Dice LR. Measures of the amount of ecologic association between species. Ecology. 1945;26(3):297–302.
30. Assaf AV, Zanin L, Meneghim MC, Pereira AC, Ambrosano GMB. Comparison of reproducibility measurements for calibration of dental caries epidemiological surveys. Cad Saúde Pública. 2006;22(9):1901–7.
31. ten Bosch JJ, Angmar-Månsson B. Characterization and validation of diagnostic methods. Monogr Oral Sci. 2000;17:174–89.
32. Nyvad B. Diagnosis versus detection of caries. Caries Res. 2004;38:192–8.
33. Henderson AR. Assessing test accuracy and its clinical consequences: a primer for receiver operating characteristic curve analysis. Ann Clin Biochem. 1993;30:521–39.
34. Fyffe HE, Deery C, Nugent ZJ, Nuttall NM, Pitts NB. Effect of diagnostic threshold on the validity and reliability of epidemiological caries diagnosis using the Dundee Selectable Threshold Method for caries diagnosis (DSTM). Community Dent Oral Epidemiol. 2000;28:42–51.
35. Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. Health Technol Assess. 2007;11(50):iii, ix–51.
36. Yerushalmy J. Statistical problems in assessing methods of diagnostic diagnosis with special reference to x-ray techniques. Public Health Rep. 1947;62:1432–49.
37. Altman DG, Bland JM. Diagnostic testes 1: sensitivity and specificity. BMJ. 1994;308:1552.
38. Brenner H, Gefeller O. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. Stat Med. 1997;16(9):981–91.
39. Porta M. A dictionary of epidemiology. 6th ed. New York: Oxford; 2014. 343 p. ISBN 978-01-99976-73-7.
40. Altman DG, Bland JM. Diagnostic tests 2: predictive values. BMJ. 1994;309:102.
41. Bonita R, Beaglehole R, Kjellström T. Basic epidemiology. 2nd ed. Geneva: WHO Press; 2006. 212 p. ISBN 978-92-4-154707-9.
42. Hausen H. Caries prediction – state of the art. Community Dent Oral Epidemiol. 1997;25:87–96.

43. Zweig MH, Campbell G. Receiver-Operating Characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem. 1993;39(4):561–77.
44. Šimundić AM. Measures of diagnostic accuracy: basic definitions. EJIFCC. 2009 Jan;19(4):203–11.
45. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3: 32–5.
46. Fluss R, Faraqgi D, Reiser B. Estimation of the Youden index and its associated cutoff point. Biom J. 2005;47(4):458–72.
47. Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF. Youden index and optimal cut-point estimated from observations affected by a lower limit of detection. Biom J. 2008;50(3):419–30.
48. Martinez EZ, Louzada-Neto F, Pereira BB. A curva ROC para testes diagnósticos. Cad Saúde Pública. 2003;11(1):7–31.
49. Altman DG, Bland JM. Diagnostic tests 3: receiver operating characteristic plots. BMJ. 1994;309:188.
50. da Silva RP, Assaf AV, Pereira SM, Mialhe FL, Ambrosano GMB, Meneghim MC, Pereira AC. Validity of caries-detection methods under epidemiological setting. Am J Dent. 2011;24: 363–6.
51. Powell LV. Caries prediction: a review of the literature. Community Dent Oral Epidemiol. 1998;26:361–71.
52. Usha C, Sathyanarayanan R. Dental caries: a complete changeover (part I). J Conserv Dent. 2009;12(2):46–54.
53. Twetman S, Axelsson S, Dahlén G, Espelid I, Mejàre I, Norlund A, Tranæus S. Adjunct methods for caries detection: a systematic review of literature. Acta Odontol Scand. 2013;71: 388–97.
54. Ekstrand KR, Gimenez T, Ferreira FR, Mendes FM, Braga MM. The international caries detection and assessment system – ICDAS: a systematic review. Caries Res. 2018;52:406–19.
55. Swets JA, Pickett RM, Whitehead SF, Getty DJ, Schnur JA, Swets JB, Freeman BA. Assessment of diagnostic technologies. Science. 1979;205(4408):753–9.
56. Neuhaus KW, Ciucchi P, Rodrigues JA, Hug I, Emerich M, Lussi A. Diagnostic performance of a new red light LED device for approximal caries detection. Laser Med Sci. 2015;30(5): 1443–7.
57. Matranga D, Campus G, Castiglia P, Strohmenger L, Solinas G. Italian deprivation index and dental caries in 12-year-old children: a multilevel Bayesian analysis. Caries Res. 2014;48:584–93.
58. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, Irwig L, Levine D, Reitsma JB, de Vet HCW, Bossuyt PMM. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6:e012799.
59. Kottner J, Audige L, Brorson S, et al. Guidelines for reporting reliability and agreement studies (GRRAS) were proposed. J Clin Epidemiol. 2011;64(1):96–106.
60. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Radiology. 2015;277(3):826–32.
61. Peeling RW, Holmes KK, Mabey D, Ronald A. Rapid tests for sexually transmitted infections (STIs): the way forward. Sex Transm Infect. 2006;82(Suppl. V):v1–6.
62. Kosack CS, Page AL, Klatser PR. A guide to aid the selection of diagnostic tests. Bull World Health Organ. 2017;95:639–45.
63. Miot HA. Sample size in clinical and experimental trials. J Vasc Bras. 2011;10:275–8.
64. Whiting P, Rutjes AWS, Reitsma JB, Glas AS, Bossuyt PMM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med. 2004;140: 189–202.
65. Norlund A, Axelsson S, Dahlén G, Espelid I, Mejàre I, Tranaeus S, Twetman S. Economic aspects of the detection of occlusal dentine caries. Acta Odontol Scand. 2009;67:38–43.

Quantitative Bias Analysis in Dental Research

Murthy N. Mittinty

Contents

33.1 Introduction – 496

33.2 Do We Require Bias Analysis? – 496
33.2.1 When Is Bias Analysis Not Essential? – 497
33.2.2 When Do We Essentially Require Bias Analysis? – 497

33.3 When to Plan Bias Analysis? – 497

33.4 What Are the Different Forms of Bias Analyses and Which One to Study? – 497
33.4.1 Selection Bias – 498
33.4.2 Unmeasured Confounding – 499
33.4.3 Information/Misclassification/Measurement Bias – 499

33.5 Example – 500

33.6 Presenting the Results from Bias Analysis – 502

33.7 Conclusion – 503

Appendix A: Stata Code for Conducting the Bias Analysis – 503

Appendix B: R Code for Plots – 504

References – 504

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_33

Core Message

Total error in a study is the sum of sampling errors and non-sampling errors. Sampling errors are also referred to as random errors and non-sampling errors as systematic errors. Generally when people present results from scientific studies, they talk about random errors. Random errors tend to diminish with an increase in the sample size, thus raising a concern about systematic errors. Systematic errors (often referred to as bias), unlike random errors, do not decrease with an increase in the sample size. Methods for addressing bias in observational epidemiologic studies have existed from the times of Berkson but have never been a regular part of dental teaching and hence are rarely implemented. The aim of this chapter is to provide the missing guidance on when and how to conduct bias analysis in dental research. Additionally, we also provide guidance on how to interpret and present the estimates of uncertainty arising from systematic errors and combat overconfidence in research results.

33

33.1 Introduction

Analysis using observational data is susceptible to two types of error: random error and systematic error. Random error is also known as sampling error. Random/sampling error reduces to zero as the sample size increases. The best way to measure random error in an associational study is to estimate the precision, where precision is measured as the inverse of variance. In contrast, systematic error never decreases to zero with an increase in sample size. This type of error is referred to as bias. One may now ask the question that when we estimate the parameter of interest (e.g. mean) and then present the confidence intervals (CI), are we not also talking about systematic error? The answer is "No"; all we are doing is presenting the random error around the estimate. This is because of how we compute the CI. Under the normal assumption, $\text{CI} = \text{mean of the parameter of interest} \pm \frac{Z_\alpha \sigma}{\sqrt{n}}$, what we are using here is σ, the standard deviation, which is a measure of the precision and the value of normal distribution when the level of significance is alpha and the sample size, n. From this formula, it is clear that we are not taking systematic error into account. Now the questions are what then is bias analysis and how do we do it. Before going into the details of answering these questions, we can start with a definition of bias.

Let's say the true value of the parameter of interest (e.g. mean, effect measure, correlation) in the population is θ; of course this might be unknown or at times known (e.g. through pilot studies or simulations). However what we have is the data on hand, and using this, we intend to estimate this parameter of interest. Let's denote the estimated parameter by $\hat{\theta}$ (read as theta hat) or also written as $E(\theta)$. Now there are three possibilities:

$$\theta = \hat{\theta} \tag{33.1}$$

$$\theta < \hat{\theta} \tag{33.2}$$

$$\theta > \hat{\theta} \tag{33.3}$$

When the possibility is (33.1), then we say the estimate is unbiased; when it is possibility (33.2), we say that the estimate is an underestimate of the true parameter; and the last one (possibility 33.3) is an overestimate of the parameter. If it is Case (33.1), nothing much needs to be done with the analysis. Unfortunately with any real data analysis, it will more likely be either Case (33.2) or Case (33.3). Moreover, when we say that the estimate is unbiased, we might be referring to it as unbiased with respect to the precision estimation. However, the validity of the estimate still remains a question. Following the above logic, we may now define bias as the difference in the true parameter and its expected/estimated value, denoted mathematically as:

Bias (B):

$$B = \theta - E(\theta)$$

The aim of this chapter is to present methods for conducting bias analysis. In this chapter, I intend to answer the following questions: Do we require bias analysis? At what stage of analysis do we need to plan the conduct of bias analysis? What are the types of bias analysis? Which bias analysis do we need to conduct? And how do we present and interpret the analysis? In addition to these, I will also present a practical example and provide some Stata code, as well as describe the other available software in statistical programs such as R, SAS and Excel. The remaining part of this chapter is organised as follows: in ▶ Sect. 33.2, I will present the reasons for the conduct of bias analysis; ▶ Sect. 33.3 illustrates when to plan for bias analysis; ▶ Sect. 33.4 presents the types of bias analysis; and ▶ Sect. 33.5 illustrates the proper conduct of bias analysis using a real example. Lastly, I give some ideas around interpreting and presenting the results from the bias analysis.

33.2 Do We Require Bias Analysis?

There are two sub-questions to this section: (1) when is bias analysis not essential and (2) when do we essentially require bias analysis?

33.2.1 When Is Bias Analysis Not Essential?

As pointed in Lash (2014), bias analysis is not essential when the intention of the researcher is just to present a description of the study but not to make any causal inference or other forms of inference. Unfortunately this is not the case with many scientific studies as they would prefer to make causal or other inferences. Another situation where a bias analysis may be helpful but not essential is when the study does not intend making causal inferences but instead offers alternative explanations for observations. Bias analysis may not be essential in situations where the random errors are so large such that the mean of the effect estimate is so small (say, e.g. a relative risk of 1.5), the precision of the point estimate is in question and the confidence intervals have a null value (e.g. if the relative risk and/or the CI contain 1), and there is no suggestion in the literature that the effect size is large (say, e.g. a relative risk of 5). Even if one satisfies themselves that bias was absent, the results from such studies can still be questionable considering the precision of the estimate. However in such studies, bias analysis may still be required, but not essential, to make substantive conclusions beyond the original study of interest. Bias analysis may be unnecessary when the observed associations are consistent with other studies and coherent to the point that the bias analysis seems unreasonable or muddying the goals.

33.2.2 When Do We Essentially Require Bias Analysis?

Bias analysis becomes essential when the goal is to make policy recommendations from the point estimates or when the estimates are required in simple decision-making. It is important to note that these decisions can be sensitive to biases. In other words, the estimation of bias is essential when the intention of the researcher is to make inferences beyond the immediate data sets and to envisage that alternative hypotheses exist. In some situations, simple associations make one believe that the current study on hand is capable of discriminating among possible important alternative hypotheses, for example, when we have a lower limit of relative risk above 1 and the upper limit of the CI is close to 2 [1]. However on conducting bias analysis, one may find that these results do not seem to hold. In such situations, it becomes essential to conduct bias analysis. One might get an impression that bias analysis must only be conducted when the interest is in policy decisions – that is not true. Bias analysis can be essential when we want to make simple decisions such as the continued collection of new data [1]. Bias analysis can also provide evidence for conducting further research on the question of interest. Therefore, based on this observation, we can definitely say that bias analysis is essential in all the studies that we conduct in oral epidemiology.

33.3 When to Plan Bias Analysis?

Similar to how we think of the sample size and power computations right at the start of the study, it is a good practice to think about the conduct of bias analysis right at the beginning of the study or project. The process of conducting a well-designed bias analysis is not only about knowing the methods used to the conduct of the bias analysis but also about knowing what information needs to be collected for the conduct of a proper bias analysis [1, 2]. That is, one needs to identify the threats to the validity of the study right at the design stage of the study. For example, let's look at the missing data – it is a threat to the validity of studies; however until recently it was a common practice to drop the missing data from the analysis, work with only complete cases and make inferences using the complete sample. However nowadays, there is a growing push from both journal editors and reviewers to explain how missing data have been handled. It is due to this push that we are noticing that researchers are taking proper measures to accommodate missing data analysis, not only during the analysis stage but also right at the design stage of their experiments or surveys [3]. Let's take another example of recall bias – this usually occurs when participants in a study are systematically less likely to recollect information relating to their outcome, dependent on the exposure. A suitable example for this situation would be about the activities that children did during the week/last month in life course analysis. To avoid recall bias, studies could ask respondents to keep diaries with a narrower focus and clear questioning. Similar steps need to be taken with other forms of systematic errors right at the beginning of the study, not after the data has been collected. We need some rules similar to CONSORT in randomised control trials or STROBE in observational studies.

33.4 What Are the Different Forms of Bias Analyses and Which One to Study?

Having learnt that bias analysis is essential and knowing that it must be designed at the start, the logical step in the process is then to know what the bias analysis does to the conventional estimate and what are the different forms of bias analyses? Firstly we discuss what the bias does. Bias analysis modifies a conventional (e.g. simple regression beta coefficient, risk difference, risk ratio) estimate of association to account for systematic error. The

equations of bias analysis have parameters referred to as bias parameters that ultimately determine the direction and magnitude of the estimate. The second aspect is to know the different forms of biases for which these parameters are being defined. There are several forms of biases that need to be addressed: bias due to unmeasured confounders, misclassification bias, recall bias/information bias, measurement error and missing data; more details on these can be found in the quantitative bias analysis book by Lash [1]. The bias parameters now allow us to make inference in regard to the direction and magnitude of selection bias, unmeasured confounding and information bias. Having seen the various forms of biases, the question then is whether we need a single bias analysis or multiple bias analysis. I exclude this discussion here but would recommend reading Chaps. 11 and 12 in Lash [1] for more on this.

33.4.1 Selection Bias

Nowadays all studies have consent processes at which time some of the selected (eligible) participants tend to refuse to respond. This is one of the side effects of requiring the consent of respondents. Refusing to respond can create bias due to loss of information, but it is essential to give an ethical choice to participants when disclosing their personal information to third parties. However, we as data analysts and designers of studies need to anticipate these biases right at the start of the study and design ways to overcome them. Let's see what could be the side effects in terms of not participating in a selected study. Not participating in a study can create two forms of missing: unit missing and item missing. Unit missing occurs when the respondent selected is not available at home (e.g. for personal interviews or telephone interviews). Item missing/nonresponse occurs when the respondent has agreed to participate in the survey or study and then decides not to respond to certain parts of the questionnaire or certain periods of the study if longitudinal. The first form of missing data (unit nonresponse) will create loss of information for the entire data collection period/questionnaire. There are several ways to reduce bias from missing/nonresponse. This type of missingness is usually anticipated at the data collection or design phase. In large surveys such as demographic health surveys, where data are collected using personal interviews, usually the data-collecting organisations are instructed to conduct three minimum visits (or telephone calls) to the household at various times to check if they can locate the respondent. If they cannot make contact with them, they can then make clear notes on the whereabouts of the respondents by asking their neighbours who may provide information about their whereabouts. Interviewers are clearly instructed not to replace the selected household with another as that can create bias. Sometimes if there are a large proportion of people from selected households who are not present during the survey period, then measures are taken to redraw the sample or reschedule the data collection time to another suitable time. It is for these reasons one needs to anticipate such hurdles right at the design phase – not once the data is being collected or after the data is collected.

Now let's look at handling item nonresponse. Item nonresponse is not as challenging compared to unit nonresponse because we have some information about the participant. This helps us to know who the refusers are; for example, let's say a participant has responded to the section on background characteristics and has not responded to some questions on child immunisation. Now if we look at the pattern of the people who have/have not responded to the child immunisation section, we can now uncover information on refusers to immunisation. It is for these reasons we can say item nonresponse can be informative. Having looked at the usefulness of data with item nonresponse, let's see what could be the possible reasons for item nonresponse. One reason as stated above could be people refusing to respond to a section. The other possible reasons could be that there is a skip pattern that one needed to follow; for example, let's say the study is interested in collecting the height and weight of the children under 8 years. Now say the selected household has two children and the first child is 10 years; for this child, the information will not be recorded and has item nonresponse. However, there can also be instances where both children are in the study age groups, but the information is not recorded – one possible reason is the child may be sick. It is for these reasons one must think of all possibilities and should ask the interviewer to collect such information that could be useful when analysing the data and studying bias. Despite taking all measures, one can still end up having item nonresponse. Item nonresponse once again creates bias in the estimate as the refusers to surveys, trials or studies can be completely different to those of the participants. Rubin [4] has described some methods to impute missing data. These methods are derived under three useful assumptions, namely, missing completely at random, missing at random and not missing at random. Details are once again not provided here, but one can read the book *Statistical Inference Using Missing Data* [5] for a detailed discussion on these methods.

To explain simply, imputation allows one to create what-if scenarios for the missing data. Now using these imputed (complete+ missing values imputed) data, one can make inferences on each of the imputed data sets and then combine the estimates from each data set to make the final inference. For example, let's say we have missing data on an outcome and some covariates, so we

impute data on outcome and these covariates. The following are the steps one needs to follow to make inference from imputed data:

- *Step 1*: Impute missing data on the outcome and covariates under the missing at random (MAR) assumption.
- *Step 2*: Let's say the parameter of interest is a risk ratio. Now using each of the imputed data sets in Step 1, we conduct a regression, say log binomial and estimate the coefficient of the exposure on the outcome.
- *Step 3*: We combine the estimates of the regression coefficients, just by simply taking the mean from each of the imputed data sets using Rubin's rules.
- *Step 4*: We take the exponentiation of the coefficient computed in Step 3. We now get the relative risk estimate from the combined data sets.
- *Step 5*: To compute the variance of the combined estimate, we take the mean of the standard errors computed in each regression conducted using each of the imputed data sets. Then we take the variance of the regression coefficient computed from each of the imputed data sets. Once again using Rubin's rules, we combine both these variances to make the total variance. The first variance, which is the mean of the variances, tells us about the variance within each of the imputed data sets, and the second variance calculated from the regression coefficients tells us the variance due to imputation.
- *Step 6*: Using the variance computed in Step 5, one can compute the confidence interval.

In doing so, what we have done is acknowledge that there are two bits of variance: variance from the completely observed cases and the variance due to imputation. Additionally, we also acknowledge that the imputed values are not true values. One question here can be as follows: how many data sets does one need to create? According to Little and Rubin [5], five imputed data sets would be sufficient. However, in epidemiology, Sterne et al. [6] recommend imputing 20 data sets. There is no rule of thumb as such, but it would be good to fix these things right at the start of the study to be consistent and state these to retain transparency and repeatability of the test.

All statistical software include methods for imputing missing data and combining the estimates from the imputed data. These methods include multiple imputation (MI) by chained equations (MICE), also known as fully conditional imputation (FCI), and multivariate normal imputation (MNI). MICE or FCI allows us to impute missing data following the distribution of the variable. For example, if the variable with missing information is binary, we use logistic regression to impute; if the variable is categorical, we use multinomial logistic regression to impute and so on. In Stata or SAS, these are referred to as MI or Proc MI libraries. Some of the literature on missing data and imputation and some limitations and cautions are Lee and Carlin [7], Lee and Simpson [8] and Allison [9].

33.4.2 Unmeasured Confounding

In causal analysis, confounders are the variables that affect both the exposure and the outcome. Studies that collect information with a special interest may collect data on aspects that are relevant to make inference. However, many studies use information from administrative data sets, registry data and surveys. These data sets do not collect information with a special interest in research but are a routine source for collecting data. When these data sets are used for research or policy-relevant decision-making, we learn that information on the exposure of interest, some confounders and the outcome is available but not available on all the possible confounders. When we use only observed confounders in such cases, we create a form of bias in the estimate, which is referred to as unmeasured confounder bias. Some of the recent methods such as directed acyclic graphs [10–12] allow us to identify those variables that may sit in the pathway of the exposure or outcome; some might be common causes. This form of bias can usually be identified at the start of the study, and we can note that this information is missing from the entire study. However, we can gather information from external studies. In order to collect information, the correct question then to ask is what sort of information one needs to conduct bias analysis for these studies. To conduct bias analysis in the presence of unmeasured confounder, one requires an estimate of the strength of association between the confounder and the outcome, the strength of association between the confounder and the exposure and the prevalence of the confounder in the exposure. As one can see, such information is usually available from external data sets. However, when we have studies conducted for the first time, one might not have any information on these parameters. In such cases, one can assign educated guesses as to their values. Multiple scenarios can be developed using such educated guesses, and hypothetical scenarios can be created for estimating uncertainty in the conventional estimate predicted using the observed confounders alone.

33.4.3 Information/Misclassification/ Measurement Bias

Misclassification refers to measurement error in categorical variables; if the variables are continuous, the error is referred to as measurement error. Measurement

error in any type of variable would lead to information bias. Misclassification is created when the analyst does not have a direct measure of the variable, but a continuous version of the variable is collected. This continuous variable is then dichotomised at the analysis stage. A form of measurement error is, for example, when we ask the participant their age – some round the age or state a year above or below their age. Another example is when we ask the mother the weight of their baby when they were born – they may provide an imprecise answer based on their recollection which creates [1] recall bias and also [2] an incorrect measure of the weight. Both of these forms of error create information bias. When the variable is continuous, and it is an exposure or a confounder, and these variables have measurement error, this can create bias in the estimate of their effect on the outcome. However when the measurement error is in the outcome, then the bias is not actually in the estimate of the effect of confounders on the outcome but the standard error of the estimate of the effect. In other words, let's say we are interested in the risk difference estimate which is computed using a simple linear regression. Now let's suppose the exposure or the confounders are mismeasured – then the bias is in the actual estimate of the risk difference. However if we say the exposures and confounders are not mismeasured but the outcome is mismeasured, in that case the bias is not in the estimate of the risk difference but in the estimate of the standard error of the risk difference [13, 14].

On the other hand, when it comes to binary/categorical variables, if the exposure or confounders or the outcomes are misclassified, then the bias is both in the estimate of the risk ratios [13–16] and their standard errors. The logical question now to ask is what information do we need to handle information bias. One way to check for misclassification bias, especially when we dichotomise a continuous variable, is to reclassify it using a new definition and check if the estimates differ and the standard errors also change. If the estimates do not change, then it is robust to misclassification; however if the estimates change, then one needs to be watchful.

It is easy to conduct bias analysis using internal data where available. Another example of using internal data might be the case where one might have taken three measurements of blood pressure. All three are recorded in the data set and are available for the analyst; in such cases, instead of using either the average of the three, one can conduct sensitivity analysis using all three measurements. In other situations one might require external data; when that is the case, one needs to know what sort of information does one need to collect. In case of misclassification, one requires information on the sensitivity and specificity of disease classification. Sometimes external data is available and at times not available. When information is not available, then an educated guess can be made, and bias analyses can be conducted using various scenarios (for more details, refer to Lash [1, 17]). Some of the useful software for addressing misclassification and measurement error can be SIMEX in R, Stata and SAS. SIMEX allows for both misclassification and measurement error. There are also some special libraries for misclassification (refer to Gustafson). Some of the interesting works regarding misclassification are by Greenland [18], Cole and Greenland [19] where they use imputation methods. Another book that would be of interest may be Rothman, Greenland and Lash [20].

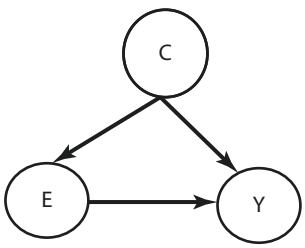
33.5 Example

Illustration of conducting bias analysis for unmeasured confounding.

Let's say we want to estimate the effect of tooth decay on impaired sleeping. Additionally we identify some of the common causes/confounders of tooth decay and family income such as years of education, age, gender, race and region of residence. Let's draw a DAG to depict the relationship and see how it can aid us in showing what would be the confounders we have and what are missing. Here the exposure (E) is tooth decay, the outcome (Y) is impaired sleeping and the above confounders (**C**) are vectors.

We can note from the DAG that the confounders listed above cannot be all the causes of tooth decay and impaired sleeping. There might be a variety of other causes that are not listed here but which can be potential causes of tooth decay (e.g. sinus infection) and impaired sleeping. The DAG with unmeasured confounders (*U*) is depicted in ◘ Figs. 33.1 and 33.2.

Using this example, we now illustrate how to conduct bias analysis for the presence of unmeasured confounders. For this illustration, I am ignoring the fact that we have missing data and then we might have misclassified impaired sleeping. Nevertheless, there is a possibility that the confounders are also mismeasured or misclassified. For example, we have included "age of the respondent" as a confounder, and we know for certain that age is often misreported. Let's say the respondent



◘ **Fig. 33.1** Directed acyclic graph depicting the relation between tooth decay (E) and impaired sleeping (Y)

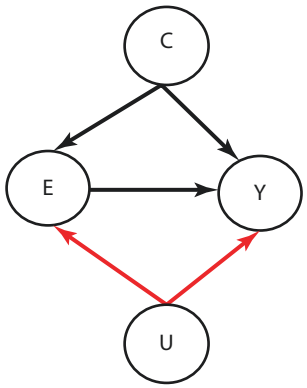


Fig. 33.2 DAG depicting the presence of unmeasured confounders of tooth decay and impaired sleeping

has lost their birth certificate and they do not remember the year of birth but they provide a hint of some landmark incidences (like the year that they were born, World War II ended). From this, an approximate age can be calculated but which then can lead to mismeasurement. Some might not have birth records if they are adopted, and some respondents may have digit preference when they report age. All of these situations can cause misclassification in confounders such as age. This is similar to the number of years of education; again there is a possibility of reporting bias which can lead to misclassification or mismeasurement. Similarly family income is rarely reported correctly by both high- and low-income earners due to concerns regarding taxation purposes. Once again, I reiterate that I have ignored all these adjustments in this illustration. Yet one can immediately identify what the problems are with the chosen variables. It is for this reason one needs to plan bias analysis right at the start of the study. As one may note from here, there can be several bias analyses. Before conducting the bias analysis for unmeasured confounder, let's see what the question of interest is and how the variables are coded. We are interested in estimating the effect of tooth decay on sleep impairment. In the data set, we have tooth decay that is coded as binary "1 – Yes tooth decay" and "0 – No tooth decay" and sleep impairment is "1 – Yes sleep impairment" and "0 – No sleep impairment". Since the outcome is binary, one can use logistic regression for rare events or log binomial to estimate relative risk. The confounder age is recorded as "12" (years) since this information is for all 12-year-old children, and we can therefore exclude this from analysis as the data is already all 12-year-olds. For the remaining confounders, gender is "1 – Male", "2 – Female"; and region is a categorical variable with five categories: "1 – North", "2 – North East", "3 – South", "4 – South East" and "5 – Central". Race is a categorical variable (1 – White, 2 – Afro descent, 3 – Asian, 4 – Mixed and 5 – Indigenous), family income is categorised as high and low and years of education above the national standard is treated as a continuous variable. Initially we will conduct our risk analysis as usual, using the log binomial regression to estimate relative risk. The results from this regression analysis are presented in Table 33.1.

Table 33.1 Estimated relative risk of toothache on impaired sleeping adjusted for confounders such as race, region, gender, education and income

Variable	Effect measure	Std. error	*p*-Value
Toothache			
Yes	5.68	0.59	<0.001
Gender			
Female	1.08	0.10	0.375
Race			
Afro descent	1.19	0.22	0.344
Asian descent	1.69	0.55	0.102
Mixed descent	1.62	0.19	<0.001
Indigenous descent	2.41	0.89	0.017
Region			
North East	0.90	0.12	0.425
South East	0.84	0.13	0.234
South	1.05	0.19	0.750
Central	1.42	0.19	0.007
Education			
Years of study	0.94	0.03	0.038
Income			
Low	1.39	0.15	0.020

From Table 33.1, we note that the relative risk is 5.68, implying that people with toothache have a five times higher risk of impaired sleeping compared to people with no toothache. However, we have not taken into account the unmeasured confounder and its effect. Let's see how we can conduct a bias analysis. First step here is to know the formula for adjusting the risk and then what information we require for conducting the bias analysis. The adjusted risk ratio is given by [1, 21–23]:

$$\mathrm{RR}_{\mathrm{adj}} = \frac{\mathrm{RR}_{\mathrm{obs}}\left(\mathrm{RR}_{UY}p_0 + (1-p_0)\right)}{\mathrm{RR}_{UY}p_1 + (1-p_1)} \tag{33.4}$$

where $\mathrm{RR}_{\mathrm{obs}}$ is the estimated risk from the data, RR_{UY} is the risk ratio associating the unmeasured confounder (U) with the outcome impaired sleeping (assuming no effect measure modification by the exposure) and p_1 and p_0 are the prevalence of confounders within the exposed

and unexposed groups (other forms of this formula can be found in Schneeweiss et al. [23]). Since these values cannot be computed from the observed data, these are called the "bias parameters". Information on the bias parameters either can be obtained from external data sets or can be gestimates (guess estimates). For illustration purposes, let's say we have obtained the values of bias parameters from external data as:

where the prevalence of sinus among respondents with toothache is 0.6, the prevalence of sinus among respondents with no toothache is 0.45 and the relative risk of sinus infections on impaired sleeping is 3.2 [24]. The relative risk computed from the observed data as estimated is 5.683. Now, the adjusted relative risk computed using Eq. (33.4) is:

$$\mathrm{RR}_{\mathrm{adj}} = \frac{5.683\left(3.2*0.45+\left(1-0.45\right)\right)}{3.2*0.6+\left(1-.6\right)} = 4.87$$

In the above computation, we have assumed that there is no effect measure modification. That is, we are not assuming that the risk of sinus infections on sleeping does not differ within the levels of toothache. If there is effect measure modification, then the equation [4] must be written as:

$$\mathrm{RR}_{\mathrm{adj}} = \frac{\mathrm{RR}_{\mathrm{obs}}\left(\mathrm{RR}_{UY_0}p_0+\left(1-p_0\right)\right)}{\mathrm{RR}_{UY_1}p_1+\left(1-p_1\right)} \qquad (33.5)$$

where RR_{UY1} and $\mathrm{RR}_{\mathrm{UY0}}$ are the bias parameters corresponding to the risk between sinus infections and impaired sleeping within toothache respondents and no toothache respondents. Now, as you may note from Eq. 33.5, we need information on additional bias parameters (RR_{UY0}, RR_{UY1}, p_0, p_1) compared to parameters listed in Table 33.2. One benefit of conducting bias analysis is it provides protection from overstating the risk. The data used for this example and the Stata code are given in the supplement.

Looking at Eqs. 4 and 5, one might assume that the bias parameters need to be scalars. That is not true – the bias parameters can be vectors. For example, suppose a systematic review is conducted to collect information on the relation between sinus infections, toothache and impaired sleeping. Now the systematic review presents us with different values of the risk of unmeasured confounder on the outcome (i.e., $\mathrm{RR}_{\mathrm{UY}}$ is a vector instead of scalar). Then the uncertainty around the adjusted relative risk can be presented using a graph as shown in Fig. 33.3. The R code for drawing the plot is given in ▶ Appendix B.

More details on computing the adjusted risks for the polytomous confounders can be found in Lash (p. 75) [1]. Computing the adjusted risk for risk difference is also detailed on page 71 of Lash [1].

Table 33.2 Bias parameters for single bias analysis of the association between toothache (*E*) and impaired sleeping (*Y*) stratified by an unmeasured confounder being sinus (*U*)

Bias parameters	Description	Values assigned to the bias parameter
$\mathrm{RR}_{\mathrm{UY}}$	Association between having sinus and impaired sleeping	3.2
p_1	Prevalence of sinus among respondents suffering from toothache in the last 6 months	0.6
p_0	Prevalence of sinus among respondents not suffering from toothache in the last 6 months	0.45

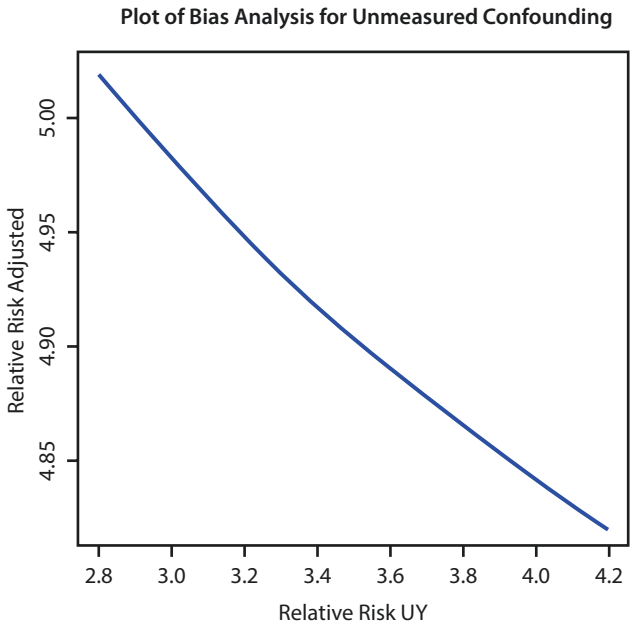


Fig. 33.3 Plot of bias analysis when the estimate of relative risk ($\mathrm{RR}_{\mathrm{UY}}$) between sinus (U) and impaired sleeping (Y) risk differs across studies

33.6 Presenting the Results from Bias Analysis

Conducting bias analysis is not a regular practice in epidemiology in general and oral epidemiology in particular. It is for this reason there is no good or bad practice when it comes to presenting the results from bias analysis. However, a good practice to implement would be to start with a clear description of the objective of conducting bias analysis. When describing the objectives, it will be useful, for example, if the analyst starts

with sentences such as "The objective of bias analysis is to evaluate the influence of exposure misclassification". That is, the regular methods section of any published work must contain a section with the purpose of conducting bias analysis and also the methods used for conducting the bias analysis. This must contain the proper formula used (e.g. Eq. 33.4). In the results section of the paper, one can describe a table similar to Table 33.2 in this chapter, to show the values of the bias parameters used. In cases where a distribution of values is used, one can either present a range or the mean and the standard error of the distribution so that users might be able to reproduce the results. It is always a good practice to share code. There must be a clear description on the biases addressed; for example, did the analyst account for unmeasured confounding and/or misclassification and/or missing data? The presentation of bias analysis must allow the user to trace from the objective to the bias model, the values assigned to bias parameters and finally the output presented. In essence, the user/reader must be able to pick the values presented in published works, be able to conduct the bias analysis independently and arrive at the same numbers presented in the published work. Presenting bias analysis must be as common as presenting unadjusted and adjusted parameters in the regression for the case when the bias parameters are scalars. However when the analyst has a distribution of values, then either it can be presented as a graph or in the form of multiple tables.

Sometimes the analyst and the researcher might think that the main focus of their research is not on the bias analysis but on the subject matter as such. In those cases, the bias analysis can be presented as supplements as many journals allow online supplements to be of any length. Alternatively, the researcher might think that bias analysis is important to present, but due to space and word limitation in research publications, it cannot be done. It will be good even in such cases to mention about bias analysis in the main paper and direct the reader to the online supplement where the results and bias analysis methods are presented. In addition to how to present and what to present, we must also make it a practice to describe the external validation data. That is, we must clearly state where the external data for bias parameters was obtained; for example, "We conducted a systematic review of the literature to identify published estimates of the distribution of the confounder in the population". When presenting input from experts, it would be useful to include statements such as "Information about the bias parameters and their distributions are educated guesses". However one thing must be remembered when using educated guesses – experts are often influenced by their selective knowledge, reading and interpretation of literature as well as personal preference. They could be overconfident and understate the uncertainty or bias [1, 17]. One has to be careful when using expert opinions for this reason.

33.7 Conclusion

In this chapter, I made an attempt to introduce quantitative bias analysis. In this attempt, I have presented some ideas around possible reasons for conducting bias analysis and planning bias analysis right at the start of the study rather than as an afterthought. The methods presented here must not be treated as comprehensive but as introductory. There is a vast amount of literature on each of the topic listed here. What have been captured here are some ideas around simple bias analyses. What is not captured here is discussion around probabilistic bias analysis, multiple bias analyses, in-depth discussions on imputation methodologies or inference using imputed data. For more details on statistical inference with missing data, refer to the works of Little and Rubin [4, 5, 25]. For a comprehensive review on quantitative bias analysis, refer to the methods described in "Applying quantitative bias analysis to epidemiologic data", Lash [1]. More on bias analysis can be found in "Modern Epidemiology" [20] .

Appendix A: Stata Code for Conducting the Bias Analysis

```
*Stata Code for conducting bias analysis
of unmeasured confounding
*Confounders income, gender, race,
education, region of residence.
*Exposure: Tooth decay
*Outcome: Impaired sleeping.
*Code prepared by Murthy N Mittinty
*Conducting some descriptives
*rename the variables
rename tootache_6mnths toothache
recode toothache (1=1) (2=2) (8/9=.)
recode familyincome (1/2=1) (3/7=2)
tab1 region gender race familyincome
yearsofstudy toothache impairedsleeping

table toothache impairedsleeping
glm impairedsleeping i.toothache i.gender
i.race ib2.familyincome yearsofstudy,
family(binomial) link(log) eform
vce(robust)

* Bias parameters
sca RR_UY=3.2
sca p_1=0.6
sca p_0=0.45
sca RR_obs=exp(_b[1.toothache])
sca RR_adjusted= RR_obs*((RR_
UY*p_0+(1-p_0))/
(RR_UY*p_1+(1-p_1)))
```

Appendix B: R Code for Plots

```
#RRo: Relative risk computed from the data
on hand
#RRuy: Relative risk between unmeasured
confounder and outcome user supplied
#p0: prevalence of unmeasured confounder
in exposed, user supplied parameter
#p1: Prevalence of unmeasured confounder
in unexposed, user supplied paramter
########################################
RRadj<-function(RRo,RRuy,p0,p1){
k<-length(RRuy)
if(k==1){
RRadju<-RRo*((RRuy*p0+(1-p0))/
(RRuy*p1+(1-p1)))
}
if(k>1){
RRadju<-0
for(i in 1:k){
RRadju[i]<-RRo*((RRuy[i]*p0+(1-p0))/
(RRuy[i]*p1+(1-p1)))
}
}
return(RRadju)
}
###################################
#The above function check if the user
supplied value of RRuy is single value or
multiple values
#and spits out the adjusted risk for a
scalar or vector valued
###################################

RRo<-5.769 #computed from data
p0<-0.45 #user supplied
p1<-0.6 #user supplied
RRuy<-seq(2.8,4.2,0.05) #user supplied
from systematic review
RRa<-RRadj(RRo,RRuy,p0,p1)

#graphing plot
plot(RRuy,RRa,type="l", col="blue",
xlab="Relative Risk UY", ylab="Relative
Risk Adjusted", main="Plot of Bias
Analysis for Unmeasured Confounding")
```

Points of Emphasis

- Bias is defined as the distance between the estimated parameter and the truth.
- What is usually unknown is how the data are generated and what is the model that fits well for the data on hand?
- Under both these uncertainties, analyses predictive or causal are carried out.
- It is for this reason conduct of sensitivity analysis, under both these forms (predictive and causal) of data analysis, becomes important.
- In additional to the above reasons, there is also another reason why sensitivity analysis is important. That is because of unmeasured confounders.
- The sensitivity analysis is all about the bias in the estimated parameter.

References

1. Lash TL, Fox MP, Fink AK. Applying quantitative bias analysis to epidemiologic data. Springer Science & Business Media; New York, 2011.
2. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol. 1996;25(6):1107–16.
3. Kish L. Statistical design for research. Wiley; New York, 2004.
4. Rubin DB. Inference and missing data. Biometrika. 1976;63(3):581–92.
5. Little RJ, Rubin DB. Statistical analysis with missing data. Wiley; Hoboken, NJ, 2014.
6. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
7. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. Am J Epidemiol. 2010;171(5):624–32.
8. Lee KJ, Simpson JA. Introduction to multiple imputation for dealing with missing data. Respirology. 2014;19(2):162–7.
9. Allison PD. Missing data. Sage Publications; Thousand Oaks, CA, 2001.
10. Merchant AT, Pitiphat W. Directed acyclic graphs (DAGs): an aid to assess confounding in dental research. Community Dent Oral Epidemiol. 2002;30(6):399–404.
11. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8(1):70.
12. Weng H-Y, Hsueh Y-H, Messam LLM, Hertz-Picciotto I. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. Am J Epidemiol. 2009;169(10):1182–90.
13. Carroll RJ, Ruppert D, Crainiceanu CM, Stefanski LA. Measurement error in nonlinear models: a modern perspective. Chapman and Hall/CRC; Boca Raton, FL, 2006.
14. Fuller WA. Measurement error models. Wiley; New York, 2009.
15. Lyles RH, Lin J. Sensitivity analysis for misclassification in logistic regression via likelihood methods and predictive value weighting. Stat Med. 2010;29(22):2297–309.
16. Lyles RH, Tang L, Superak HM, King CC, Celentano DD, Lo Y, et al. Validation data-based adjustments for outcome misclassification in logistic regression: an illustration. Epidemiology (Cambridge, Mass). 2011;22(4):589.
17. Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. Int J Epidemiol. 2014;43(6):1969–85.
18. Greenland S. The effect of misclassification in the presence of covariates. Am J Epidemiol. 1980;112(4):564–9.
19. Cole SR, Chu H, Greenland S. Multiple-imputation for measurement-error correction. Int J Epidemiol. 2006;35(4):1074–81.

20. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008.
21. Bross ID. Spurious effects from an extraneous variable. J Clin Epidemiol. 1966;19(6):637–47.
22. Schlesselman JJ. Assessing effects of confounding variables. Am J Epidemiol. 1978;108(1):3–8.
23. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf. 2006;15(5):291–303.
24. Bengtsson C, Lindberg E, Jonsson L, Holmström M, Sundbom F, Hedner J, et al. Chronic rhinosinusitis impairs sleep quality: results of the GA2LEN study. Sleep. 2016;40(1):zsw021.
25. Little RJ. A test of missing completely at random for multivariate data with missing values. J Am Stat Assoc. 1988;83(404):1198–202.

Reviews Systematic and Meta-analysis

Roger Keller Celeste and Falk Schwendicke

Contents

34.1 Introduction – 508

34.2 Systematic Reviews – 508
34.2.1 Reviews of Observational Studies: Controversies, Reality and Needs – 509

34.3 Resources – 510

34.4 Control and/or Assessment of Possible Biases and Appropriate Use of Meta-analysis – 511
34.4.1 The Control of Bias in the Process of Data Collection – 511

34.5 Data Synthesis: Meta- and Network Meta-Analysis – 514
34.5.1 Treatment Effects in Meta-Analysis – 514
34.5.2 Network Meta-Analysis – 518
34.5.3 Synthesis of Data for Observational Studies – 520

34.6 Applying Systematic Review Techniques for Health Economics or Implementation Research – 520

34.7 Conclusions – 521

References – 521

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5_34

Learning Objectives

- Learn the difference between systematic and narrative reviews.
- Understand the impact of bias in systematic reviews.
- Understand difficulties in systematic reviews of observational studies.
- Deal with heterogeneity in meta-analysis.
- Understand principals of network meta-analysis.

34.1 Introduction

Efforts to synthesize scientific evidence date back centuries, but the methodology for systematic reviews has only been refined in recent decades, particularly in the social and health sciences. These methods focus on reduce systematic errors or bias, providing a rigorous, reliable and comprehensive answer towards a particular question [1]. The most obvious manifestation of this trend is the long-standing growth of the Cochrane Collaboration (▶ www.cochrane.org), an international organization that prepares, maintains and disseminates rigorous systematic reviews [2].

The number of scientific articles grows exponentially [3], while the growth of systematic reviews in health sciences has even superseded that systematic reviews are now more common than narrative reviews in dentistry [4]. While the total number of articles indexed in the PubMed database increased 2.4 times from 2000 to 2017 (from 528,000 to 1.279.714 publications), the number of articles with the words "systematic review" in the title increased by 457 times (from 278 to 127.060 publications). Traditionally, systematic reviews have been a compilation of the best evidence available; and this has involved almost exclusively intervention studies, like randomized clinical trials. However, the need and utility of systematic reviews of observational studies (e.g. cross-sectional, case-control, cohort) are increasingly recognized. In 2000 it was estimated that 42% of the published meta-analyses included observational studies [5], and these trends have continued.

In this chapter, we will not describe step by step how to carry out a systematic review, as this methodology is well described in other specific textbooks and especially in the handbook the Cochrane Collaboration [6]. Instead, we will discuss reviews of observational studies and focus on possible sources of bias, which should be controlled at each stage of the review process, and on the appropriate use of meta-analysis in systematic reviews of randomized controlled trials but also observational studies. We will further provide ample room for linking our remarks to other freely available resources, which can be used as detailed guidelines for the conduct and dissemination of systematic reviews on health interventions. This chapter concludes with a perspective on how systematic review data can inform health economics and implementation science.

34.2 Systematic Reviews

What, then, is a "systematic review", and why should this term be distinguished from the term "meta-analysis"?

> The term "systematic review" denotes a type of scientific study that seeks to gather and examine all studies carried out on a specific question in order to provide an unbiased summary of the evidence, following a predefined, comprehensive and objective approach.

Systematic reviews must describe a replicable method of locating, evaluating and synthesizing evidence from relevant primary studies in order to obtain valid answers to specific questions. Unlike narrative reviews that do not adhere to an explicit method and can therefore be open to bias and significant random error, systematic reviews tend to avoid these pitfalls by providing an objective summary of the available evidence. It is common for some reviews to report the search strategy, but this report does not characterize a review as "systematic" if other issues highlighted in ◘ Fig. 34.1 are not part of the review. Thus, systematic reviews often require more time, resources, skills and collaboration than "narrative" (or traditional) reviews, as can be seen by comparing their main characteristics (▶ Box 34.1). Systematic reviews follow a structured approach, encompassing several steps (◘ Fig. 34.1).

Box 34.1 Comparison between systematic and narrative reviews (adapted from [7, 8])

Feature	Systematic review	Narrative review
Question	Clear, focused on one facet of a problem	General, encompassing different aspects of a topic
Search	Tries to find published and unpublished studies, to limit the impact of publication and other types of bias	Documentation of the search strategy is rarely reported, potentially biased

Feature	Systematic review	Narrative review
Selection	Clear description of the inclusion criteria to limit selection bias	Rarely specified and potentially subject to bias
Quality assessment	Systematically examines the methods used in primary studies and assess risk of bias	Not always considers differences in the methods and quality of the studies
Data extraction	Replicated, pilot tested extraction form. Attempts to obtain published and unpublished data	Not objective and reproducible
Synthesis	Quantitative summary, when appropriate, is useful	Qualitative summary; quantitative summary inappropriate
Conclusions	Based on pooled, mainly clinical evidence	Not always based on direct clinical evidence, sometimes based on theory or indirect evidence from animals or laboratory studies

When a systematic review includes several studies that used the same metric, it can employ a statistical technique called "meta-analysis" to quantitatively combine the results of similar studies.

A meta-analysis, however, only describes a possible, but particularly important, component of systematic reviews, since many systematic reviews culminate in a meta-analysis. The meta-analysis, however, still allows for extensions beyond the simple calculation of a combined effect estimate, such as the formal evaluation of factors that may affect clinical outcomes.

34.2.1 Reviews of Observational Studies: Controversies, Reality and Needs

Synthesizing the evidence from observational studies, for example, on the association between disease onset and risk factors, or on the distribution and occurrence of diseases, etc., is also potentially useful. The global burden of disease studies provide a good example of how powerful analyses of observational studies can be,

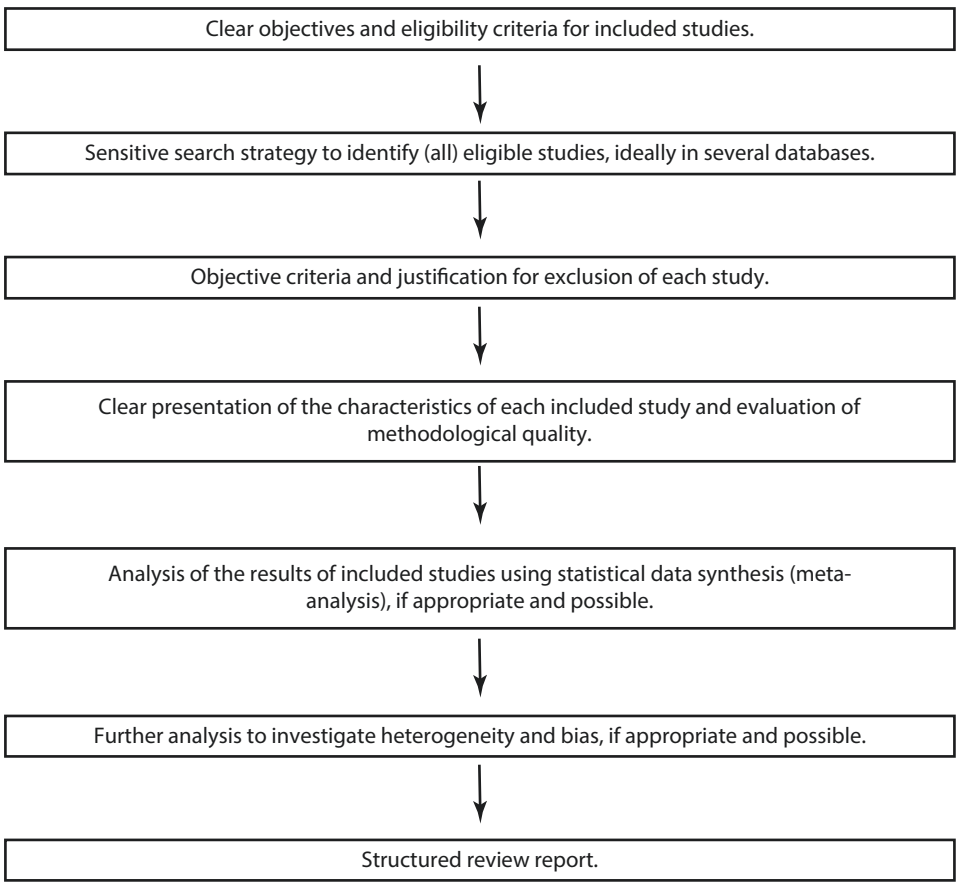


Fig. 34.1 Fundamental characteristics (or steps) of a systematic review

how versatile their application has become and how much impact on health policy such reviews may eventually have [9]. The website of the Institute for Health Metrics and Evaluation provides details of their methodology and GBD studies (► http://www.healthdata.org).

However, there has been some controversy over the utility of systematic reviews of observational studies (e.g. cross-sectional, case-control, cohort). Some authors even reject such reviews, based on the risk to come to potentially non-valid (false positive or negative) findings [10, 11]. However, these arguments apply to reviews of interventional studies, too; they hence apply to any systematic review; its quality is never better than the quality of the included studies, and rigorous methodology is key [12, 13].

> The limitations of observational studies are well-known, and systematic reviews of such studies should be interpreted accordingly. No observational study, large or small, can exclude the possibility of some bias or the presence of confounding situations.

Some results from large and convincing systematic reviews of observational studies were not confirmed in subsequent randomized controlled trials. An example is the case of postmenopausal hormone replacement with oestrogen, in which a review pointed to a protective effect (RR = 0.58, 95% CI 0.48–0.69) for cardiovascular disease [14]. Subsequent randomized clinical trial showed that the effect could even be the opposite (RR = 1.24, 95% CI 1.00–1.54) [15].

In dentistry, there is a similar situation. In the early 1990s, it was proposed that subclinical infections with gram-positive bacteria could stimulate inflammatory mediators in pregnant women, causing premature labour [16]. One study presented empirical evidence of the association of preterm birth and periodontal disease [17], and in the following years, a profusion of studies was published, and systematic reviews pointed to a possible, although not clear, association [18–20]. Later, a large randomized clinical trial showed that the treatment of destructive periodontal disease in pregnant women was not associated with the reduction of low birth weight [21] and the high risk of erroneous conclusions due to spurious findings confirmed by a systematic review and meta-analysis [22].

In public health, the need for systematic reviews of observational studies is clear for several reasons. The main one, perhaps, is the very existence of many published observational studies; assessing all of them is difficult for the single researcher. Also, systematic reviews may allow comparing findings from studies and contrasting them, hence revealing aspects that cannot be seen individually in each study. On one hand, it is also said that many decisions in public health cannot be made on the basis of controlled trials [23], either because of the practical difficulties of carrying them out (e.g. large-scale social interventions) or ethical impediments (e.g. study of etiological factors). On another hand, the possibility of controlled trials in public health is strongly encouraged by MacIntyre [24], who advocates in favour of controlled community trials to evaluate health promotion actions. Yet, even if public health policies start using more controlled community trials, policy-makers will still have to rely on observational studies (and systematic reviews of observation studies) until enough evidence appears.

34.3 Resources

During the last decades, essential (and up-to-date) guidelines have been created to assist with systematic reviews and meta-analyses [25, 26]. Many valuable resources are freely available and include online courses available in different languages. This is mainly due to the work of the Cochrane Collaboration (► www.cochrane.org) and its centres in 43 countries (► https://www.cochrane.org/about-us/our-global-community). The collaboration purpose is to produce high-quality systematic reviews in health. Initially, Cochrane Collaboration included only intervention reviews (therapeutic or preventive), but currently it further includes reviews for diagnostic test accuracy, methodology, qualitative and prognosis studies. The Cochrane Reviewers' Handbook is the official Cochrane Collaboration document that details the entire process of creating systematic Cochrane reviews. It is available on the website:

► https://training.cochrane.org/handbook

In addition to the Cochrane Reviewers' Handbook, the open learning material for Cochrane Collaboration reviewers is a convenient set of modules available online for each stage of a Cochrane systematic review. It is available on the website:

► https://training.cochrane.org/interactivelearning

The guide of the NHS Centre for Review and Dissemination [25] produced in the United Kingdom is freely available at:

► https://www.york.ac.uk/crd/training-services

An initiative to register systematic review protocols is a valuable resource to find ongoing reviews and avoid your review to be duplicated. It further enhances the methodological rigour of the review, as the methods, including search sequence, inclusion criteria and outcomes, etc. need to be registered a priori. Cochrane reviews are always registered, while for other reviews, researchers can register their review at:

► https://www.crd.york.ac.uk/prospero/

From the statistical software point of view, there are several commercial software packages available, but we highlight two free ones, where online tutorials are available: R, a freely available software, provides packages for meta-analysis, ***meta*** and ***rmeta*** [27], and ***metafor*** for meta-regression [28]. The Cochrane Collaboration software Reviewer Manager (latest version RevMan 5.3 for Mac, Linux and Windows) is intended for preparing reviews, also non-Cochrane reviews, and allows meta-analysis, too. Its download is available at:

► https://community.cochrane.org/help/tools-and-software/revman-5

Finally, guidelines have been produced to assist in how to report systematic reviews. The most well-known are the PRISMA [29] statement (preferred reporting items for systematic reviews and meta-analyses) and the MOOSE [30] statement (meta-analysis of observational studies in epidemiology) for observational studies. Further useful resources can be found at:

► www.equator-network.or

34.4 Control and/or Assessment of Possible Biases and Appropriate Use of Meta-analysis

When conducting systematic reviews, researchers deal with both systematic errors (bias) and random errors. Especially when meta-analysis is applied, the latter are of a lesser concern; pooling studies, each coming with a randomly directed error, will to some considerable degree mitigate the effects of random errors [31]. The larger issue is, usually, systematic errors; as pooling studies does not compensate for bias, there is a need for scientific rigour throughout the entire process of a systematic review to assess and minimize possible systematic errors. This is complex and requires many judgments. Nevertheless, the basic scientific principles underlying the process of conducting a systematic review are similar to those of any other study: formulation of the specific problem to be addressed; identification and access to "a population" through information sources; extraction and analysis of data; and careful interpretation and description of results. Detailed guidelines were developed to assist in the control of bias in the conduct of systematic reviews and in the appropriate use of meta-analysis [25, 26]. Note that in the following sections, we do not discuss the individual biases found in each included study, like performance or detection bias, but rather biases on a review level, which can be introduced or mitigate by the reviewer herself or himself.

34.4.1 The Control of Bias in the Process of Data Collection

The validity of the results obtained in a systematic review is dependent on the methods that will be used during the process of data collection. This covers the methods used to identify the studies to be included in the review, to determine the eligibility of the studies for inclusion, to assess the quality of these studies, and to extract data. Bias can be introduced in any of these phases (► Box 34.2).

Box 34.2 Bias in included studies and results of a systematic review (adapted [32, 33])

Possible sources of bias in different stages of the review
I. Publication bias Selective submission Selective acceptance
II. Identification bias (bias in the location of studies)
Database bias
Language bias
Citations bias
Multiple publications bias
III. Selection bias
Inclusion criteria bias
Quality score bias (selector bias)
IV. Bias at getting data
Extractor bias
Selective reporting bias

The most critical feature of any systematic review of randomized controlled trials is to identify and include all relevant studies of acceptable quality for the analysis [34]. In particular, it should cover unpublished studies, as relevant studies may not have been published for reasons related to their own results [35]. The outcome of unpublished, not identified, or identified but not included studies may differ systematically from those finally included. Therefore, as general rule, researchers should avoid limits to year or language of publication.

34.4.1.1 Publication and Identification Bias

It is likely that a systematic review that is restricted to published evidence will produce misleading results due to "publication bias", i.e. selective publication of studies with positive, i.e. statistically significant results [36,

37]. This may lead to distorted findings and over-optimistic estimates from meta-analysis because of omitted data.

Selective submission for publication rather than selective acceptance by scientific journals seems to be the dominant factor in publication bias [36, 37]. However, regardless of the possible causes of "publication bias", prior registration of clinical trials is considered the most satisfactory remedy for this type of bias [35, 38, 39], with each prospective trial being registered upfront, hence allowing to screen through the registry databases will allow to capture concluded, but not published trials.

Approximately 25% to 50% of the randomized clinical trials are not published, and approximately 50% of conference abstracts reporting the results of controlled trials are not also published as complete studies [40, 41]. These figures emphasize the importance and the magnitude of the efforts required to find unpublished material relevant to possible inclusion in systematic reviews in order to minimize the effects of "publication bias".

Direct contact with investigators can help in the identification of studies. Access to non-formally published yet available literature, the so-called "grey literature", by searching specialized databases (e.g. opengrey.eu) or by directly checking research reports and dissertations, and selecting abstracts from scientific conferences and meetings, should also be attempted.

However, even when studies are formally published, some may be more difficult to identify than others. It is necessary to search on a variety of bibliographic databases, since the exclusive use of MEDLINE from the National Library of Medicine, for example, may leave out a significant proportion of relevant studies [40, 42]. In addition, it is difficult to identify studies published in non-indexed journals, in particular those that are not published in English. A search in other library databases, such as PsycINFO, EMBASE or those at Virtual Library of Health – which includes SciELO and LILACS – could improve the identification of studies in other languages and journals not indexed in MEDLINE [40, 43]. The Cochrane Controlled Trials Register (CENTRAL) should always be used, too. It is currently recognized as the best electronic source for controlled clinical trials and includes unpublished and ongoing studies. Nevertheless, the risk of "English language bias" and "database bias" indicates that a high proportion of clinical trials with no statistically significant or no statistically significant results are only published in other languages (not English) or in non-indexed scientific journals [33].

Citation databases (e.g. Scopus and Web of Science) and list of references of review articles should also be examined. However, studies with statistically significant results are usually more cited [44] and published repeatedly [45], leading to, respectively, "citation bias" and "publication bias multiple" [33]. Such biases make it even more likely that positive studies will be localized and included in systematic reviews. In addition, since it is not always obvious that multiple publications come from a single study, repeated inclusion of data in a systematic review may lead to inflated effects in meta-analysis [45]. An additional strategy provided by citation databases is to track citing articles from included studies. Finally, the use of Google Scholar, although might help, is not advisable because results cannot be replicated.

34.4.1.2 Bias in the Selection and Quality Evaluation of the Studies

Eligibility criteria defined a priori for the selection of studies should be consistent with the focus of the review. These criteria should be explicit and based directly on the intervention, population, outcomes, comparisons and type of primary study to be included (in relation to the study design) and methodological standards. Differences in populations, interventions or exposures, outcomes and methods of study that define inclusion criteria, as well as differences in search strategies used to identify studies, may lead to the inclusion of different studies and therefore the possibility of discrepancies in the results of systematic reviews that seem to address a similar research question. Chalmers et al. [46] conducted a study that addresses the replication of meta-analysis of controlled trials and found that there were cases where different conclusions were reached for the same intervention, although some of these discrepancies arose from the choice of outcome measures.

The search strategy should, especially for observational studies, be rather sensitive than specific (restrictive), as many of these studies are not well indexed and missed, for example, if too many search terms are combined. If a large number of studies are eventually included, this will allow for subgroup or meta-regression analysis, hence contributing to understanding differences between studies, and will also support the strength of any conclusion from the review [33]. For constructing the search strategy, but more so to define inclusion criteria, the use of the PICO(S) strategy (i.e. selecting vocabulary based on population, intervention, control, outcome and, sometimes, study type) is recommended.

The evaluation of the quality of each selected studies is adamant, mainly as studies with low quality also often come with distorted numerical findings, hence distorting the overall conclusions from the review [47, 48]. Assessing study quality may further help to understand heterogeneity [49]. Although randomized controlled trials (RCTs) are considered the best evidence on the effec-

tiveness of health interventions, this type of study is not immune to bias. The biases in RCTs can be reflected in systematic differences between the comparison groups in the characteristics of the participants (selection bias), in the care of the participants (which should be the same for all groups) or in the exposure to other factors besides the intervention of interest (performance bias), in the verification of outcomes (detection bias) and in the occurrence and control of losses or exclusions of participants included in the study (follow-up or exclusion bias). To assess the quality of randomized trials, the Cochrane Risk of Bias tools can be used, for example [50]. For non-randomized interventions, alternatives are also available [51]. For observational study, further aspects like selection or measurement bias and lack of control for confounding variables arise [52]; the Newcastle-Ottawa scale [53] is a widely used tool to assess risk of bias in such studies.

Excluding studies due to quality reasons is seldom advisable; instead, sensitivity analysis (e.g. with only low risk studies being retained) can be performed to gauge the impact of study quality. Methods for incorporating quality assessments based on a "quality score" are also inadvisable because they will be affected by the problems inherent in the use of any composite scale. There is support for using simple methods to individually evaluate relevant methodological aspects of a study and explore their influence on the magnitude of the effects [12].

34.4.1.3 Data Extraction Bias

In a systematic review, there are two levels of data extraction. The first concerns data to evaluate whether the identified study is eligible for inclusion. And, for eligible studies, a second level refers to data related to relevant outcomes and participant characteristics, interventions, study quality and other relevant characteristics for qualitative and, if appropriate, quantitative synthesis. Although data can be collected in various ways, previously tested forms (tested in potentially included articles) for data extraction should be used. Ideally, two observers should extract all data, independent of each other, to avoid errors. Masking the extractors with respect to authors' names and their institutions, names of biomedical journals, funding sources and acknowledgments, may increase consistency to the process and reduce bias [54], although additional work and costs need to be considered as it is difficult to get a completely masked data extraction [55].

Although tedious, it is desirable to extract as much information as possible. Thus, the effect of "publication bias" is minimized, ambiguities in the methods are clarified, and auxiliary analyses (subgroup or meta-regression analysis) become possible [34]. Unpublished information obtained should be extracted in exactly the same way as published information [31, 39]. Data extraction is usually easier in more recently published than non-published or very old studies, mainly as more recently published studies usually follow the Consolidated Standards for Describing Controlled Trials (CONSORT) [56].

34.4.1.4 Bias in Systematic Reviews of Observation Studies

Among the bias described so far, some are more frequent in observational studies. For example, the selective reporting bias, and to some extent the submission bias, deserve attention. Selective report of some associations arises from exploratory techniques that use solely statistical criteria to select variables into analytical models, such as stepwise methods or data mining. Also, data extraction is often more complex in observational studies; and many decisions made by the original authors for presenting their findings can only be accepted in hindsight (e.g. choice of models, outcome measures, cut-offs, etc. cannot be changed in most cases except when contacting the original authors and re-analysing their dataset).

Warning

Unlike clinical trials, which test a priori hypotheses, observational studies are quite often exploratory by their nature. Taking national health surveys as an example, the amount of variables in the dataset makes the number of pairwise association enormous, but the sample size is rarely calculated to test any specific statistical association. Hence, both false-positive and false-negative findings are often likely. Similarly, claim databases and data from health surveillance systems provide huge sample sizes, where even minute associations easily reach statistical significance. Researchers should safeguard themselves against such effects and conduct association analysis based on a theory, i.e. a construct of why such association may occur, and should conduct sensitivity analysis and multivariable, i.e. model-based assessments, in addition to bivariate analysis.

Finally, the quality of observational studies is a potential bias, and it is not possible to guarantee the absence of confounding situation in any specific study. Therefore, the exclusion of observation studies based on methodological quality is usually not indicated. The use of quality scales such as the Newcastle-Ottawa Scale [53] may be an alternative, as previously mentioned, to assist in interpretation of findings. Stratified analyses or meta-regression may further help to overcome or understand heterogeneity or possible inconsistencies.

34.5 Data Synthesis: Meta- and Network Meta-Analysis

The analysis and summary of the data that are collected for a systematic review concerns the process of systematically evaluating and integrating the results of the included studies, first qualitatively, and then often through quantitative synthesis [57]. Synthesis will often use tables and descriptive analysis of included studies to gauge the general characteristics of included studies, their samples, settings and methods. If possible, statistical synthesis by meta-analysis or meta-regression can then follow. We will first describe some general aspects towards meta-analysis and present methods used in conventional pairwise meta-analyses. These, traditionally, compare the effects of two interventions across different studies (they analyse the results of these studies on a meta-level, hence meta-analysis). We will then describe statistical methods to measure and assess reasons of heterogeneity across studies, mainly by tabulation and meta-regression, followed by a presentation of further methods to compare multiple interventions (the so-called network meta-analysis) as well as methods more often found for synthesizing observational studies. Note that this field is growing quickly, and new methods emerge fast.

34.5.1 Treatment Effects in Meta-Analysis

An important principle in the meta-analysis of RCTs is that although individuals in a randomized trial should be directly comparable, the same cannot be said for individuals included in different randomized trials. This results in two difficulties; (1) the results have to be obtained, in a first step, separately for each study, and expressed in a common format; this relates to the question of how to measure treatment effects. (2) A second aspect is that trials may not be comparable with each other and that a synthesis will hence not yield consistent results or will suffer from high heterogeneity; this will be discussed later on.

The choice of the "treatment effect" measure – that is, the estimate of the observed relationship between an intervention and an outcome, expressed, for example, in terms of odds ratio (OR), relative risk (RR), absolute risk reduction (ARR), number needed to treat (NNT), standardized difference of means or weighted difference of means – will depend on the type of outcome measure used (such as dichotomous, continuous, ordinal, survival). However, regardless of the type of outcome, the choice between absolute or relative "treatment effect" measures will depend on theoretical considerations, such as their mathematical properties; the stability of the analysis between studies and subgroups and the ease of interpreting the results. In general, it is more sensible to use relative measures of effect to statistically compile the evidence and perform analyses (e.g. odds ratios, relative risk) and absolute measures of effect to apply the results clinically or in public health (e.g. risk difference, number needed to treat). If, for example, assessing the relative risks of tooth loss in periodontitis patient cohorts, the absolute effects estimates will demonstrate that treatment effects are, overall, relatively limited, while the relative comparisons between treatments may not suggest so. The reason for this is that overall, the risk of tooth loss is low (in most cohorts, an average periodontitis patient loses 0.1–0.2 teeth per year), and a 30% decrease or increase in this risk may come with only very limited absolute changes in tooth loss rates.

For dichotomous outcomes, the "odds ratio" may be the preferred outcome measure for the meta-analysis because of its convenient mathematical properties. Notably, though, "odds ratio" differs from "relative risk" if the event is common (it inflates, i.e. suggests treatment differences to be larger), and relative risks are more intuitively understandable to most people. If the results are homogeneous between studies, a combined "odds ratio" or a combined "relative risk" can subsequently be converted into an "absolute risk reduction" (risk difference) or the number needed to treat to yield differences between two treatments, i.e. into absolute measures [58].

Warning

When a numerical summary is not possible, avoid simple techniques, such as vote counting of publications "in favour/against" or "positive/negative results" [59]. Also avoid mere pooling of results via estimating means, etc., like mean annual failure rates for restoration, as these are often subject to severe confounding from other factors [60] (cohort that received the intervention, follow-up rate). If so, perform extensive sensitivity analysis to assess the impact of these potential confounders.

If the outcome is continuous or is treated as such (e.g. counts and long ordinal variables with >10 levels), greater care should be taken when choosing an appropriate measure of effect to compare groups. The "weighted difference of means "between the intervention group and control can be used when the outcomes are measured in the same way in each controlled trial (same scale and units), with the advantage of being able to make an obvious interpretation of the results, but with the disadvantage of being influenced by the baseline risk of the population. Although more difficult to

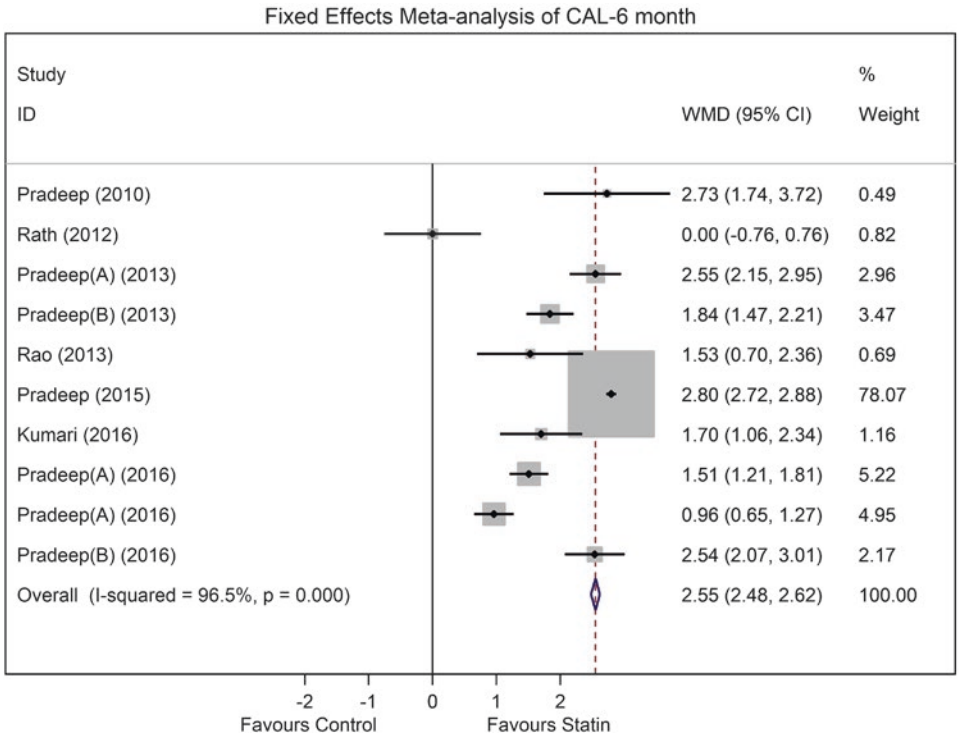


Fig. 34.2 "Forest plot" of a fixed meta-analysis of ten controlled trials comparing weighted mean difference (WMD) in the reduction of clinical attachment loss (numbers are in millimetres) of different types statins against a placebo (or no treatment) among periodontal patients [62]

interpret, the "standardized difference of means" (usually defined as the difference of means between intervention and control groups, divided by the standard deviation of the control or both groups) allows the analysis of similar outcomes that were measured differently in the controlled trials [61]. The standardized difference of means is not straightforward to understand, as it is a relative, unitless measure but overcomes the issue of different statistical scales being used across studies (which is oftentimes the case in public health studies).

Overall effects or quantitative summaries of the results of the studies included in a review can be calculated by combining statistically the data compiled from each study. Results of each study are displayed along with their confidence intervals, in a "Forest Plot", as in Fig. 34.2.

The forest plot graphically displays the effects of single studies and the pooled estimates. On the x-axis, the treatment effect is plotted, which can be odds ratios or mean differences, etc. The small black dots present the mean effect measured in each single study; each horizontal line represents the respective confidence interval (95%): the shorter the line, the more precise the result. As with most meta-analyses, studies are weighted according to their precision (the narrower the confidence interval, the larger the weight); this can also be reflected in the forest plots; with weights being expressed by the size of the study-centre quadrangles. The diamond at the bottom represents the pooled (meta-analytic) result; the wider the diamond, the wider the confidence intervals of the pooled estimates. Studies and pooled estimates right to the vertical line indicate that the test treatment, in this case statin, was beneficial. This graphical representation is simple and allows to indicate both the amount of variation in the results of the studies and the general estimate of the results of all the pooled studies [63].

34.5.1.1 The Choice of a Statistical Model for Meta-Analysis

Several statistical methods are available for synthesizing study results, but it is usual for the meta-analysis to employ the idea of combining treatment effects by calculating a weighted average of the individual effects of the studies along with their 95% confidence intervals in which larger studies have more influence (weight) than smaller ones (as described above). Statistical techniques for meta-analysis can be broadly classified into two models; the fundamental difference between them is the way in which the variability between study results is addressed.

The "fixed effects model" assumes the existence of a treatment effect common to all studies and considers that the variability between studies is exclusively due to random variation [64]. The use of this model hence works under the assumption that only the intra-study variation (intra-study sampling errors) influences the uncertainty of the results (which is reflected in the confidence interval) of a meta-analysis. In this sense, variations between the estimates of effect of each study

(heterogeneity) do not affect the confidence interval in a fixed-effect model.

The "random effects model" works under the assumptions that different studies come with different baseline risk, etc. and that included studies are a random sample from some hypothetical universe of all studies. This model takes additional variation across studies into account by calculating a common treatment effect that leads to a more balanced weighting of individual studies, giving relatively more weight to small studies than they would receive in a fixed-effects model, and usually produces wider synthesized confidence intervals [65].

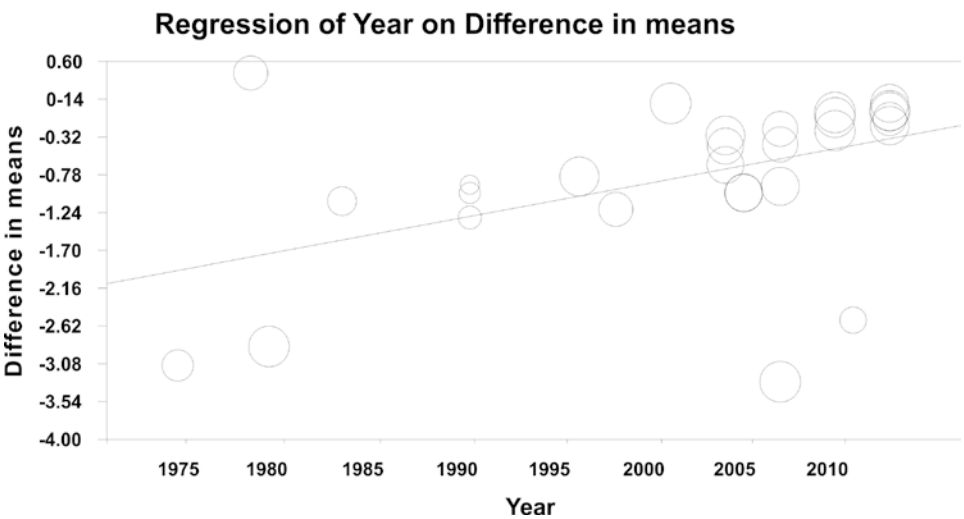
The choice of the model hence depends on the underlying assumptions but also the distribution of data. For most analyses, though, random effects models will be appropriate and yield robust results, and it is often unreasonable to assume homogeneity in public health and health research contexts [66]. Notably, though, applying random effects model should not be seen as a panacea for any situation with considerable heterogeneity [12, 67], as discussed below. In any case, sensitivity analyses, using fixed-effect models instead, may be applied to assess the impact of model choice on the results and derived conclusions.

34.5.1.2 Investigating Heterogeneity, Robustness and Bias in the Meta-Analysis

In the context of systematic reviews, heterogeneity concerns the variability or differences between studies in effect estimates. At times, a distinction is made between "statistical heterogeneity" (differences in outcomes), "methodological heterogeneity" (differences in study designs) and "clinical heterogeneity" (differences between studies in key participant characteristics interventions and outcomes). This distinction is relevant, as only the first one can be captured statistically; the second one may require methodological expertise and the third one clinical expertise. Before engaging into any kind of synthesis, all three should be explored; ideally, meta-analysists should have knowledge about the presence and magnitude of the present heterogeneity as well as the underlying reasons.

Statistical tests of heterogeneity are used to determine if the observed variability in the results is greater than the expected due to chance. However, these tests have low statistical power, due to low number of included studies. Statistical heterogeneity can also be assessed by inspection of the funnel plot. The I-square statistics estimates the percentage of the variance that is due to heterogeneity rather than chance [68], and values of above 50% are oftentimes seen as high. If heterogeneity is verified (statistically and graphically), then possible sources of differences between studies should be explored [61, 67] with respect to differences in population, interventions, outcome measures and methodological characteristics.

If a meta-analysis contains unexpected heterogeneity, one can perform meta-regression analysis when there is a large number of included studies. This analytical resource, meta-regression, is a powerful extension of the traditional meta-analysis, through which one can assess the impact of study meta-characteristics on the size of the treatment effect examined. For example, the year of publication may be tested as one possible influencing factor on the observed treatment effects. For studies on the benefits of fluoride varnish, for example, treatment effects significantly decrease with time, mainly as in more recent study caries increments decreased but also as patients in more recent studies used a number of other fluoride sources (tooth pastes, salt, etc.), hence decreasing the benefits of fluoride varnish (◘ Fig. 34.3). However, the results of such analyses should be interpreted with great caution, especially if these analyses are



◘ **Fig. 34.3** Meta-regression analysis. The prevented caries increment (in surfaces) when using fluoride varnish versus no such varnish from different systematically compiled studies was plotted against the time. The preventive effect (reduction in caries increment, y-axis) decreased towards no effect at all (difference in means of zero) over time. This effect was highly significant; the difference in means decreased by 0.04 per year. (Data from [69] submitted to meta-regression)

not determined a priori, as they suffer from the risk of false-positive detections, and if multiple meta-regressions are performed, these risks add up (alpha-inflation).

In addition or alternative to meta-regression (where the independent variables are continuously scaled), performing stratified analysis of subgroups of studies may allow exploration of heterogeneity and also yield clinically relevant subgroup effects. Again, subgroup analysis should be planned a priori because of an increased chance of a false-positive result when many subgroup analyses are performed [61].

In any case, researchers should attempt to examine the robustness (or sensitivity) of their meta-analytic results, for different assumptions and uncertainties about the data used and the results obtained. This is done through "sensitivity analyses" (analyses used to determine the sensitivity of the results of a systematic review to changes depending on different input data or applied methodologies). The most valid synthesis of available information will be obtained when descriptive summaries of results contain data on inclusion and non-inclusion of unpublished data sources, the quality of clinical trials (see above) and the choices and assumptions made in extracting data, as a form of sensitivity analysis. Caution should be exercised when interpreting the overall results of the review if it is found that its findings may be subject to certain methodological decisions (e.g. if for the fluoride varnish data shown above, studies from certain time periods would have been excluded, this may have distorted the overall findings).

In addition to sensitivity analyses, an important extension of a meta-analysis concerns the examination of publication or small-study bias, as described above. It is well-known that studies with positive results (e.g. a new therapy being significantly better than an existing standard) are more likely to be published (publication bias) and that early studies on new treatments are usually more positive than later, larger confirmatory studies (small-study bias). The latter is grounded in a number of aspects, like sample selection and sample size, lower methodological rigour in smaller earlier studies or possible bias by the first-applying researchers (e.g. sponsorship or inventor bias, academic or professional bias) but also regression to the mean in later, larger studies. Such bias will systematically distort results, usually in favour of the "new" or test group, as studies being less positive have either not seen the light of publication or have not been conducted yet.

Publication bias can be assessed graphically and statistically. Graphical assessment builds on funnel plots (Fig. 34.4). This visual resource consists of a simple graphical representation of the effect size of each included study (on the x-axis) and the sample size (on the y-axis) [70]. In the absence of bias, the results of the smaller studies will spread widely and symmetrically at the bottom of the graph (reflecting the larger uncertainty in these trials, which results in larger variability

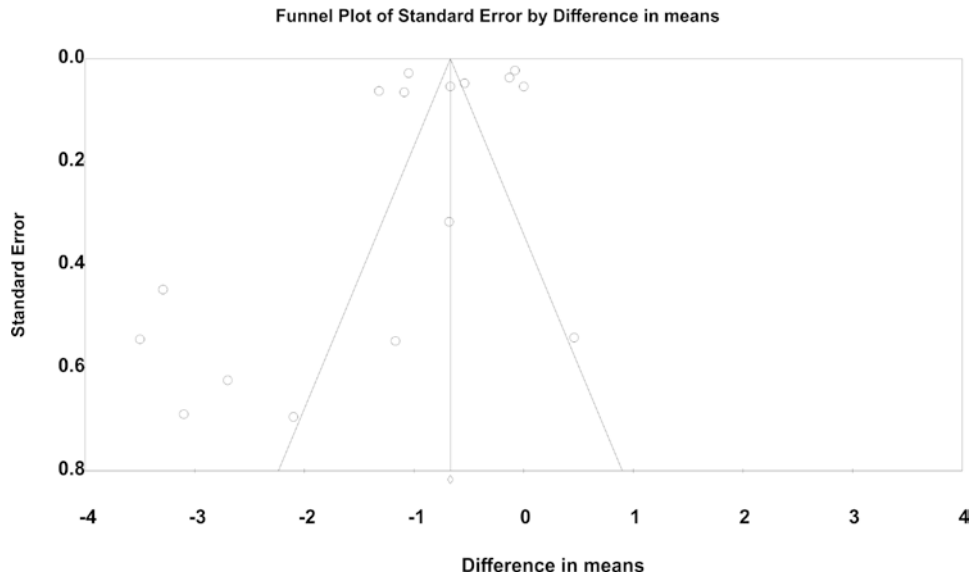


Fig. 34.4 Funnel plot, based on a subsample of the studies in Fig. 34.3, comparing fluoride varnish versus no such varnish for caries prevention. There is indication for bias, with smaller studies (at the bottom) being clearly asymmetrically distributed. The funnel is constructed around the overall mean effect of a meta-analysis, assuming this to be the true effect. The inverted standard error of each single study (indicating study sample size) is then plotted on the single study's effect estimate (difference in caries increment in the fluoride varnish versus no varnish group). The identification of over-optimistic trials and the associated risk of bias are possible. Smaller trials (which come with a larger standard error, at the lower end of the figure) show larger differences, with fluoride varnish reducing the caries increment to a much higher degree in these studies than in larger studies (with lower standard error), which converge around the tip of the funnel and the assumed true effect. Inspection of this funnel plots indicates that publication bias is likely present

around the true effect), while results from studies with larger samples will converge at the top (around the true effect). An asymmetry of the funnel indicates bias, usually with smaller, less positive studies missing (as discussed, smaller, earlier studies are usually overoptimistic and not vice versa). The funnel chart is thus a test for any type of bias that is associated with the sample.

Statistical methods that present an objective measure of asymmetry in a funnel chart are available but, as for homogeneity tests, are of limited value when only a few trials are included in the systematic review [70].

34.5.2 Network Meta-Analysis

Network meta-analysis is useful in many circumstances; as for many medical problems, multiple interventions are available. Network meta-analysis can also be applied when two interventions have been investigated by many studies but via different protocols (e.g. different doses of the same medication has been tested, etc.). In this case, these two interventions can be separated into different groups of similar dose, delivery, etc. and compared using network meta-analysis.

> Network meta-analysis is a technique which allows to compare multiple interventions, in contrast to pairwise meta-analysis.

While both the conduct and the mathematics behind network meta-analysis are beyond this chapter, a number of things need to be discussed and considered before network meta-analysis should be conducted. Network meta-analysis usually builds on a network of interventions, with most single studies only delivering information on one pairwise comparison (three-or-more-arm studies being an exception), while the multiplicity of such pairwise information then allows to infer also on comparisons across the network which have not been made (so-called indirect comparisons).

Prior and during network meta-analysis, a number of aspects should be considered, as discussed in the following.

First, the pairwise comparisons across the network should be comparable, i.e. randomization should be assumable all over the network. In many instances, this is not the case (lack of the so-called transitivity); for example, certain comparisons for preventing a condition may only be available in secondary care settings, while others are only available in primary care; certain interventions may mainly be applied in the primary, other in the permanent dentition; certain comparators may only be applicable to specific more severe subtypes of a condition, while others mainly treat milder types. These aspects have been discussed for pairwise meta-analysis, where they lead to heterogeneity. In network meta-analysis, they can lead to severe distortions, and analysts should take care to assess them a priori, for example, by tabulation (aspects like inclusion criteria and sample selection, randomization, setting, risk profile, intervention administration, outcome assessment, risk of bias) should be assessed.

Second, analysts should inspect the network carefully before engaging into further analysis and can draw a range of relevant conclusions by inspecting a network graph. Such graph is depicted in ◘ Fig. 34.5. A range of conclusions can be derived from such graphs, e.g. how many different comparators have been tested, how well connected are they (how dense is the network), how many studies form each connection, what kind of shape does the network have (polygonal networks are far less prone for erroneous conclusions during meta-analysis than chain-wise networks, where it is much harder to detect inconsistencies), etc. Recently, studies in dentistry even focused on analysing such comparator networks and found relevant information on the overall applicability of trial data, for example, in cardiology [71]. It should be noted that in any such analysis (and generally in network meta-analysis), the definition of each comparator (i.e. the comparator classification) will have large impact on the findings, and different definitions may be tested for their impact on the conclusions.

Third, a decision on how to assess, display and interpret results is needed. In network meta-analysis, a range of options for providing results is available, with different interpretability and robustness. These range from ranks (being ranked the best, second best etc.), which are easy to interpret, over pairwise comparators, which are not easy to grasp especially when many comparators are available, ranking probabilities (how likely is an intervention ranked first, second etc.), which allows to better reflect the certainty of rankings. The definition and advantages and disadvantages of different outcomes measures in network meta-analysis are shown below in ▶ Box 34.3.

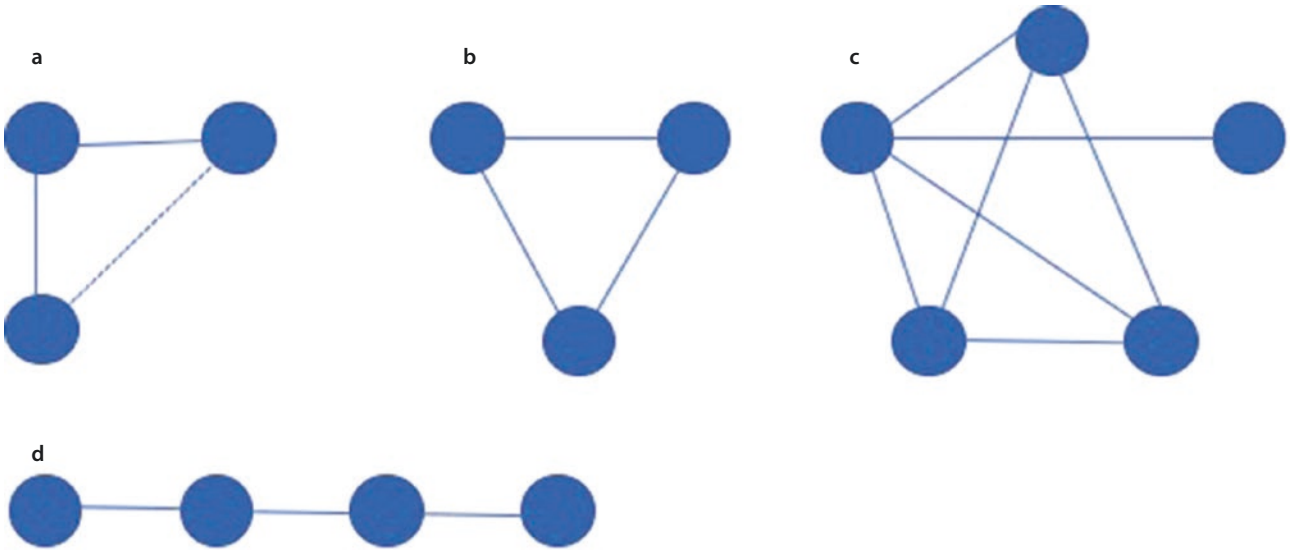


Fig. 34.5 Network configurations. (**a**) Direct evidence builds on comparisons actually made by studies (solid lines). By inference, indirect evidence (dotted line) of comparisons not made is possible. (**b**) A single closed loop network, where all possible comparisons have been made. Such network allows direct inspection of inconsistency (e.g. if intervention A is superior to B and B to C, and then A also needs to be superior to C in a pairwise comparison). (**c**) A polygonal network configuration, where many, but not all comparisons have been made; the risk of not detecting inconsistency is limited (only one node is only connected to only one other node, all other comparisons are made to two or more other nodes). (**d**) Chain-wise network configuration. This network is prone to erroneous conclusions from any network analysis, as it consists of a chain of pairwise comparisons. Detection of inconsistency is impossible, and risks of erroneous conclusions are carried over from one comparison to another, hence multiplying [72]

Box 34.3 The definition and advantages and disadvantages of different outcomes measures in network meta-analysis

Outcome measure	Definition	Advantage	Disadvantage
Rankings	A ranking of comparators based on their probability of being the best, second best, etc. intervention	Easy to communicate and interpret	High chance of false conclusions; rankings provide some certainty, while probabilities of being ranked best may be very uncertain in fact
Pairwise comparisons	A pairwise estimate for all possible direct and indirect comparisons in a network	Allows precise estimation of relative effects; if direct and indirect estimates are displayed, also allows assessment of inconsistency	Hard to assess, especially in large networks
Ranking probabilities	A plot or table displaying the chance of being ranked first, second etc. for each comparator	Displays transparently overall certainty; if appropriate graphics are used, this can also be transported in an interpretable way	Hard to assess, especially in large networks

Overall, network meta-analysis is an increasing popular tool but very sparsely applied in public health and health services research so far. In the future, it may also be employed in this field more often, while a large range of open questions as to the specific application in this field remain. In any case, there is growing and extended guidance on designing and conducting network meta-analysis.

34.5.3 Synthesis of Data for Observational Studies

Meta-analysis of data from observational studies presents more difficulties than that of clinical trials due to a number of aspects:

- Identifying all studies is usually harder, as indexing is poorer; publication bias is more likely. Therefore, it is even more necessary to assess all types of bias, as described.
- Studies from different countries will show high degree of heterogeneity in most cases due to country-level aspects; studies from different hospitals, etc. will come with the same problems (the so-called cluster effects). These should be accounted for during statistical evaluation (adjustment for cluster effects, which is beyond this chapter), and the transportability between healthcare settings should be assessed by the meta-analyst.
- The effect measured is not as clear as in interventional studies. In many cases, one tries to pool association estimates (is smoking consistently associated with tooth loss in periodontal patients?); effect measures are hence not "treatment effects" and often inconsistently measured or scaled.
- If such association estimates are pooled, they will be the result of statistical modelling itself. Different models may come with different findings; models adjusted by covariates will often report lower association estimates than only bivariate models (see above). It is preferable to use adjusted estimates for confounding factors, as they capture complex associations and display more realistic estimates than crude association estimates.
- Different scales of both the independent (e.g. smoking measured in pack years or categorically as smoker versus no/former smoker) and the outcome variable. For example, it is possible that two studies have used odds ratio to evaluate the effect of poverty on the dental caries experience, but one dichotomized the DMFT at zero (DMFT>0) and the other at 20 (DMFT>20). Alterations in the cut-off point alter the prevalence of the outcome; however, since they are two parameterizations of the same variable, the effect of poverty could be expected to be the similar. Also, relative risks, odds ratio or other measures cannot be readily pooled.
- The same data material may be analysed by different studies, usually using different analytical methods, or assessing specific population subgroups or specific years, especially from large surveys (like NHANES waves). Researchers need to take care to not enter the same data several times, as this would inflate the sample size and also lend more weight to the same study in a meta-analysis.

Overall, researchers should attempt to investigate any of these factors in depth both before conducting meta-analysis but also when synthesized results are present. Understanding how these factors modify results will usually help to understand the complexity behind the findings and enrich them significantly.

34.6 Applying Systematic Review Techniques for Health Economics or Implementation Research

Systematic review and meta-analysis data allows to inform researchers and the consumers of research about the comparative efficacy or effectiveness of interventions or about synthesized evidence from observational studies. However, it can also be applied in another context. Two popular examples are health economics and implementation research.

In health economics, systematic review data are often the basis for any economic assessment of interventions in modelling studies. In such modelling studies, researchers are able to follow individuals or individual teeth through a predetermined pathway, allowing to reflect on possible events and costs along that pathway. At each simulated cycle (which may be days, months, years, depending on the speed of events), individuals or teeth may remain in the health state they were initially placed in (e.g. healthy, a mild periodontitis patient, a restored tooth) or may translate into a next health state (e.g. diseased, a severe periodontitis patient, a broken tooth). Each translation comes with a certain chance, called transition probability (and usually, it also comes with costs, e.g. for treatment).

While, of course, researchers may assign these transition probabilities based on their own or experts' opinion (something which should only be done if no applicable data at all are available), or use data from single studies to decide on these probabilities, it is good practice to use systematically compiled, synthesized data, assuming these to be robust. Health economic modelling, hence, allows to transform systematic efficacy/effectiveness data from one context (clinical research) into another (health economics, health technology assessment) and also allows to combine them (as over a chain of events, multiple transition may occur, e.g. from a sound tooth to a carious one to a restored one to a broken one to a replaced on), each possibly being supported by a systematic review.

In addition, in implementation research, systematic reviews may be applied. While implementation research is in its first steps in dentistry, systematic reviews have already been conducted to assess, for

example, possible barriers and enablers for dentists' managing carious lesions using contemporary carious tissue removal strategies instead of the traditional "complete" (non-selective) removal [73]. Of course, meta-analysis may not be possible in all cases or for all questions (in case of this review, it was used to meta-analyse the proportion of dentists who stated to have adopted different removal strategies, and by using meta-regression, it was found that this proportion has been increasing over time). Alternative techniques like meta-synthesis may also be used. For the same review, for example, a meta-synthesis was additionally perform. Researchers used a framework called the theoretical domains framework and associated concepts form behavioural sciences to assess how the dentists' behaviour towards carious tissue removal is shaped. Multiple studies may offer different concepts, and these can be synthesized to display ambiguity or uniformity of findings but also to better understand context-specific aspects, etc. The technique of a systematic review proves to be versatile and useful in implementation science, too.

34.7 Conclusions

During the last decades, considerable scientific advances have sustained the development of medical and dental practice. The decision process that involves health care is now based on a much greater degree of information derived from research. However, there is still a significant gap between evidence from research and health policies and the clinical practice. The problem is clearly shifting from lack to information to information overload and uncertainty about how to properly use this information. The rapid introduction of new technologies, growing concerns about the costs of medical and dental care and increasing demands for a better quality of care add to this picture.

Systematic reviews are one important tool to bridge that gap by providing robust, compiled, synthesized information. So far, in public health, the number of published systematic reviews remains still relatively small [74]. In recognition of the need to develop and maintain a robust health information system, the Cochrane Collaboration Health and Public Health Field has identified priority areas of global importance and is commissioning public health reviews and of particular relevance to developing countries [75].

With emerging and refined methods to also address complex problems, using complex procedures, and the increasing acknowledgment how versatile systematic reviews and subsequent analyses derived from systematically complied data can be, the relevance of systematic reviews is likely to grow further in the future.

References

1. Chalmers I, Hedges LV, Cooper H. A brief history of research synthesis. Eval Health Prof. 2002;25:12–37.
2. Clarke M, Langhorne P. Revisiting the Cochrane collaboration. Meeting the challenge of Archie Cochrane – and facing up to some new ones. BMJ. 2001;323:821.
3. Celeste RK, Bastos JL, Faerstein E. Trends in the investigation of social determinants of health: selected themes and methods. Cad Saude Publica. 2011;27:183–9.
4. Muniz FWMG, Celeste RK, Oballe HJR, Rösing CK. Citation analysis and trends in review articles in dentistry. J Evid Based Dent Pract. 2018;18:110–8.
5. Egger M, Smith GD, Schneider M. Systematic reviews of observational studies. In: Egger M, Smith GD, Altman DG, editors. Syst. Rev. Heal. Care meta-analysis context. 2nd ed. London: BMJ Books; 2001. p. 211–27.
6. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 5.1.0. 2011.
7. Cook DJ, Greengold NL, Ellrodt AG, Weingarten SR. The relation between systematic reviews and practice guidelines. Ann Intern Med. 1997;127:210–6.
8. Petticrew M. Systematic reviews from astronomy to zoology: myths and misconceptions. BMJ. 2001;322:98–101.
9. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. J Dent Res. 2015;94:650–8.
10. Shapiro S. Meta-analysis/Shmeta-analysis. Am J Epidemiol. 1994;140:771–8.
11. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. J Clin Epidemiol. 1995;48:71–9.
12. Greenland S. Can meta-analysis be salvaged? Am J Epidemiol. 1994;140:783–7.
13. Petitti DB. Of babies and bathwater. Am J Epidemiol. 1994;140:779–82.
14. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med. 1991;20:47–63.
15. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003;349:523–34.
16. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL. A review of premature birth and subclinical infection. Am J Obs Gynecol. 1992;166:1515–28.
17. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol. 1996;67:1103–13.
18. Madianos PN, Bobetsis GA, Kinane DF. Is periodontitis associated with an increased risk of coronary heart disease and preterm and/or low birth weight births? J Clin Periodontol. 2002;29(Suppl 3):22–8.
19. Vettore MV, Lamarca Gde A, Leao AT, Thomaz FB, Sheiham A, Leal Mdo C. Periodontal infection and adverse pregnancy outcomes: a systematic review of epidemiological studies. Cad Saude Publica. 2006;22:2041–53.
20. Scannapieco FA, Bush RB, Paju S. Periodontal disease as a risk factor for adverse pregnancy outcomes. A systematic review. Ann Periodontol. 2003;8:70–8.
21. Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006;355:1885–94.
22. Schwendicke F, Karimbux N, Allareddy V, Gluud C. Periodontal treatment for preventing adverse pregnancy outcomes: a meta- and trial sequential analysis. PLoS One. 2015;10:e0129060.

23. Victora CG, Habicht J-PP, Bryce J. Evidence-based public health: moving beyond randomized trials. Am J Public Health. 2004;94:400–5.
24. Macintyre S. Good intentions and received wisdom are not good enough: the need for controlled trials in public health. J Epidemiol Commun Heal. 2010;65:564–7.
25. Khan KS, ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking systematic reviews of research on effectiveness CRD's guidance for those carrying out or commissioning reviews. In: CRD Rep. Number 4. 2nd ed. York: CRD Publications Office; 2001. p. 277.
26. Clarke M, Oxman A. Cochrane reviews will be in Medline. BMJ. 1999;319:1435.
27. Hothorn T, Everitt BS. Meta-Analysis: Nicotine Gum and Smoking Cessation and the Efficacy of BCG Vaccine in the Treatment of Tuberculosis. In: A Handbook of Statistical Analyses using R; 3rd ed CRC Press: Boca Raton; 2014. 344–361.
28. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36:1–48.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
30. Stroup DF. MOOSE statement: meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283:2008.
31. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI how to use an overview Evidence-Based Medicine Working Group. JAMA. 1994;272:1367–71.
32. Felson DT. Bias in meta-analytic research. J Clin Epidemiol. 1992;45:885–92.
33. Egger M, Smith GD. Bias in location and selection of studies. BMJ. 1998;316:61–6.
34. Clarke MJ, Stewart LA. Obtaining data from randomised controlled trials: how much do we need for reliable and informative meta-analyses? BMJ. 1994;309:1007–10.
35. Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA. 1990;263:1385–9.
36. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. JAMA. 1992;267:374–8.
37. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet (London, England). 1991;337:867–72.
38. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ. 1997;315:640–5.
39. Cook DJ, Guyatt GH, Ryan G, Clifton J, Buckingham L, Willan A, McIlroy W, Oxman AD. Should unpublished data be included in meta-analyses? Current convictions and controversies. JAMA. 1993;269:2749–53.
40. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ. 1994;309:1286–91.
41. Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. A meta-analysis. JAMA. 1994;272:158–62.
42. Hopewell S, Clarke M, Lusher A, Lefebvre C, Westby M. A comparison of handsearching versus MEDLINE searching to identify reports of randomized controlled trials. Stat Med. 2002;21:1625–34.
43. Clark OAC, Castro AA. Searching the Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS) database improves systematic reviews. Int J Epidemiol. 2002;31:112–4.
44. Gøtzsche PC. Reference bias in reports of drug trials. BMJ. 1987;295:654–6.
45. Tramèr MR, Reynolds DJ, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. BMJ. 1997;315:635–40.
46. Chalmers IG, Collins RE, Dickersin K. Controlled trials and meta-analyses can help resolve disagreements among orthopaedic surgeons. J Bone Joint Surg Br. 1992;74:641–3.
47. Sacks H, Chalmers TC, Smith H. Randomized versus historical controls for clinical trials. Am J Med. 1982;72:233–40.
48. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273:408–12.
49. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbé KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. J Clin Epidemiol. 1992;45:255–65.
50. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282:1054.
51. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
52. Mallen C, Peat G, Croft P. Quality assessment of observational studies is not commonplace in systematic reviews. J Clin Epidemiol. 2006;59:765–9.
53. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. In: Ottawa Hosp. Res. Inst. 2011. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 26 Feb 2019.
54. Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJ, Cavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
55. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. Lancet (London, England). 1997;350:185–6.
56. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet (London, England). 2001;357:1191–4.
57. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. BMJ. 2001;323:157–62.
58. Egger M, Smith GD, Sterne JAC. Uses and abuses of meta-analysis. Clin Med (Northfield Il). 2001;1:478–84.
59. Greenland S, O'Rourke K. Meta-analysis. In: Rothman KJ, Greenland S, Lash TL, editors. Mod. Epidemiol. 3rd ed. Philadelphia: Lippincott-Williams; 2008. p. 652–82.
60. Schwendicke F, Blunck U, Tu Y-K, Göstemeyer G. Does classification of composites for network meta-analyses lead to erroneous conclusions? Oper Dent. 2018;43:213–22.
61. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med. 1996;15:2733–49.
62. Muniz FWMG, Taminski K, Cavagni J, Celeste RK, Weidlich P, Rösing CK. The effect of statins on periodontal treatment—a systematic review with meta-analyses and meta-regression. Clin Oral Investig. 2018;22:671–87.
63. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. BMJ. 2001;322:1479–80.
64. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med. 1984;3:409–20.
65. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.

66. Chalmers I. The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. Ann N Y Acad Sci. 1993;703:156–63; discussion 163–5.
67. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med. 1998;17:841–56.
68. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ Br Med J. 2003;327:557–60.
69. Schwendicke F, Splieth CH, Thomson WM, Reda S, Stolpe M, Foster Page L. Cost-effectiveness of caries-preventive fluoride varnish applications in clinic settings among patients of low, moderate and high risk. Community Dent Oral Epidemiol. 2018;46:8–16.
70. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997;315:1533–7.
71. Schwendicke F, Innes N, Levey C, Lamont T, Göstemeyer G. Comparator choice in cariology trials limits conclusions on the comparative effectiveness of caries interventions. J Clin Epidemiol. 2017;89:209–17.
72. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163–71.
73. Schwendicke F, Göstemeyer G. Understanding dentists' management of deep carious lesions in permanent teeth: a systematic review and meta-analysis. Implement Sci. 2016;11:142.
74. Swingler GH, Volmink J, Ioannidis JPA. Number of published systematic reviews and global burden of disease: database analysis. BMJ. 2003;327:1083–4.
75. Waters E, Doyle J. Systematic reviews of public health in developing countries are in train. BMJ. 2004;328:585.

Supplementary Information

Index – 527

M. A. Peres et al. (eds.), *Oral Epidemiology*, Textbooks in Contemporary Dentistry,
https://doi.org/10.1007/978-3-030-50123-5

Index

A

Absolute risk reduction (ARR) 514
Accumulation of risk models 297
Adverse pregnancy outcomes (APO) 387
Airways 240
Amelogenesis imperfecta (AI) 171–173
American Board of Orthodontics Discrepancy Index (ABO DI) 81
Artificial neural networks 363
Association for Health Services Research (AHSR) 396
Attributable risk (AR) 9
Australian Research Centre for Population Oral Health, Australia (ARCPOH) index 43–45, 49

B

Backdoor path 273
Bad breath, *see* Halitosis
Barker's theory 296
Basic Erosive Wear Examination (BEWE) 216, 217
Bayes' theorem 490–492
Behavioural Model of Health Services 397, 398
Behavioural rating scale (BRS) 112
Belmont report 411
Benzoyl-DL arginine-naphthylamide (BANA) test 237
Big data
– acquisition, storage, and processing 363, 364
– attributes 358
– causal methods 361
  – assumptions 361
  – differences-in-differences 361
  – instrumental variables 361
  – machine learning (*See* Machine learning)
  – propensity score matching 361
  – regression discontinuity 361
– challenges 359, 360
– clinical decision making 359
– definition 358
– examples 359
– health policy 359
– opportunities 359
– sources 358, 359
– spurious correlations 360
Biomedical model 336
Black Report 4
– artefact 282
– behavioural/cultural explanations 282, 283
– materialist/structuralist explanations 282, 283
– neo-material theory 283
– psychosocial explanations 283
– social capital 283
– theories of natural/social selection 282
11-point box scale (BS-11) 111
British Association for the Study of Community Dentistry (BASCD) index 43, 49
Business Service Authority (BSA) 350

C

Cardiovascular diseases (CVD) 311, 385–387
Caries Assessment Spectrum, and Treatment (CAST) index 43
Carolina Abecedarian Project (ABC) 428
Carotid intima-media thickness (cIMT) 383
Causal inference
– causal diagrams 272
  – analysis 272
  – components 272, 273
  – principles 273–275
– counterfactual approach 270, 271
– definition 268
– induction and falsification 268, 269
– instrumental variables 276
– MSM 275, 276
– necessary causes 269, 270
– probabilistic causation 270, 271
– randomized control trials 275
– SEM 276
– socio-economic inequality 288, 289
– standardization and parametric G-Formula 276, 277
– statistical association 271, 272
– statistical inference 268
– sufficient-component causes 269, 270
Centers for Disease Control and Prevention 4
Child Oral Health Impact Profile (COHIP) 323
Child Perceptions Questionnaire (CPQ) 323
Cholera epidemic 4
Chromatin condensation 369
Cleft lip and palate
– embryological development 160
– environmental risk factors
  – alcohol 162
  – folic acid intake 162
  – maternal health 163
  – maternal obesity 162, 163
  – maternal stress 163
  – population attributable risk 163
  – smoking 161
  – socioeconomic status 163
– ethnicity 161
– gene-mapping 164
– gene variation 164
– genetic-environmental interactions 164
– genetic influence 164
– health outcomes 165
– International birth incidence/prevalence 160, 161
– prevalence 160
– quality of life 164, 165
– risk factors 160
– sex 161
Clínica do Tratamento do Hálito (CTH-RJ) 243, 244
Code of conduct
– Belmont Report 411
– The Declaration of Helsinki 410, 411
– Nuremberg Code 410
Collective oral health 424
Collider 273
Community periodontal index (CPI) 61
Conditional cash transfer (CCT) programs 428
Counterfactual approach 270, 271
CpG islands 370
Craniofacial growth and development 80
C-reactive protein (CRP) 383
Critical and sensitive period models 297

D

Dean index 123
Dental aesthetic index 83
Dental caries
– advantages and limitations 55
– age-standardised incidence 54
– age-standardised prevalence 54
– analysis and reporting 49–53
– ARCPOH index 43, 45
– assessment 45, 46, 48, 49
– BASCD index 43
– CAST index 43
– at cavitation level 40, 53
– in deciduous teeth 54
– definition 40
– demineralisation 40
– dental care index 42
– DMF index 41, 42
– DMFS index 41, 42
– DMFT index 40
– early childhood caries 41
– enamel and dentine 40
– epidemiology 55
– etiological and risk factors 55
– ICDAS index 43
– individual psychosocial factors 40
– intake of sugars 40
– intermediate determinants 40
– lifetime prevalence 53
– longitudinal studies 53
– macro-level social structures 40
– meso level psychosocial 40
– meso level social formation 40
– net caries increment method 42
– NHANES 45
– in permanent dentition 53, 54
– population-based cohort studies 53
– at population level 41
– proximal determinants 40
– PUFA index 43
– remineralisation 40
– root caries 41, 49, 54
– social determinants 41
– social structural macro conditions 40
– at sub-clinical stages 40
– at tooth surface level 40
Dental erosion
– advantages and disadvantages 214
– behavioral factors 211, 212
– BEWE 216, 217
– biological factors 212
– definition 210
– demographic characteristics 212, 213
– differential diagnosis 213, 214
– Eccles index 215
– epidemiological studies 210
– epidemiology of 216–218
– Erosion index 216
– and etiological factors 213
– frequency and distribution 214
– gastroesophageal reflux disorder 212
– O'Sullivan's index 216, 217
– risk factors 210
– socioeconomic factors 213
– tooth wear 210
– tooth wear index 215
– UK National Survey 216
Dental fluorosis
– aetiology and clinical appearance 122, 123
– in Australia 123
– canary in the coal mine 122
– causes of 122
– DDE Index 126
– Dean index 127
– differential diagnosis 126
– fluorosis-specific indices 126
– FRI 128–129
– measurement 126
– prevalence 122–124
– public opinion 129
– risk factors
  – fluoridated supplements 125, 126
  – fluoridated toothpaste 125
  – fluoridated water 125
  – fluoride from foods 126
– TF index 127
– TSIF 128, 129
Dental visits
– access to dental care 398
– check-up visits 400, 401
– demand/utilisation 401, 402
– family income 399
– favourable pattern 401
– independent variables 399
– inequality 399, 400
– number of visits 399
– predisposing variables 400
– problem-based visits 401
– socioeconomic demand 399
– time intervals 399
Deoxyribonucleic acid (DNA) 368
Developmental defects of enamel (DDE)
– amelogenesis imperfecta 170–173
– causes 170
– celiac disease and chronic kidney disease 171
– genetic influence 171
– hyperbilirubinaemia 171
– local causes 171
– mandibular primary canine 171
– maturation phase 170
– molar–incisor hypomineralisation 171
– in permanent teeth
  – hypomineralised defect 176
  – hypoplasia 176
  – illness and medication 177
  – maternal–child illness 176
  – molar–incisor hypomineralisation 177–179, 183, 184
  – prevalence 176
  – socio-economic status 176
  – trauma 177
– pH regulation 170
– prevalence 170
– in primary teeth
  – diffuse lesions 173
  – hypomineralised defect 173
  – hypomineralised lesions 173
  – hypomineralised primary teeth 175
  – hypomineralised second primary molars 176
  – hypoplastic enamel 173
  – infants 173–176
  – primary incisors 173
  – risk factors 173
– qualitative defect 170

– quantitative defect 170
– secretory phase 170
– transitional phase 170
Diagnostic odds ratio (DOR) 488
Dice index 485, 486
Digital pandemics 420
Dimethyl sulfide (CH3SCH3) 240
Direct path 273
Directed acyclic graphs (DAGs) 272
– analysis 272
– components 272, 273
– principles 273–275
Disability-adjusted life years (DALYs) 224
DNA methylation 368

E

Early childhood caries (ECC) 41, 302
Early Childhood Oral Health Impact Scale (ECOHIS) 323
Eccles index 215
Ecosocial epidemiology
– black box metaphor 337
– causal determinants 339, 340
– chronic non-communicable diseases 338
– classification 334
– climate change 338
– contemporary changes 338
– critical epidemiology 337
– critical tradition gain 338
– determinants 338
– ecological fallacy 343
– education, prevention and health promotion 343
– genomics, proteomics and metabolomics 338
– health-disease process 336, 337
– health practices 334
– historical evolution
  – biomedical model 336
  – causal network 335, 336
  – chronic-degenerative diseases 335
  – disease distribution 335
  – distal determinants 336
  – health outcomes 335
  – microbiology 335
  – morbidity and mortality 335
  – proximal factors 336
  – risk factors 335
  – spider-free web 336
  – tooth cavities 336
– HIV 337
– ideologization 334
– methodological frameworks 334
– oral epidemiology 340–342
– organization levels 338
– overview 334
– social health inequities 343
– theoretical frameworks 334
Edentulism 224, 226, 227
Epidemiological studies
– analogy 5
– attributable risk 9
– biological gradient 5
– biological plausibility 5
– calculation of prevalence 5
– case-control studies 8
– clinical observations and lab research 4
– coherence 5
– consistency 5
– cross-sectional and longitudinal studies 9
– definition 4
– diseases frequency measures 5–7
– error sources 19–21
– experimental evidence 5
– exposure and disease measures 8
– exposure and health outcome 5
– form of analysis and association measures 9
– Hopewood House study 4
– internal and external validity 19
– intervention or experimental studies (*See* Intervention or experimental studies)
– observational studies (*See* Observational studies)
– population attributable risk measures 9
– prevalence and incidence measure 7
– reversibility 5
– risk factor 9
– specificity 5
– standardisation of coefficients 5
– strength of association 5
– temporality 5
– typology of designs 7, 8
– Vipeholm study 4
Epigenetics 375
– architecture 368
– behaviour 372
– biomarkers 368, 375
– cancer 372
– chromatin condensation 369
– chronic periodontitis 372
– class of information 368
– coding regions 369
– CRISPR/Cas9 gene editing 375
– definition 369
– dental caries 373
– DNA methylation 370
– environmental exposure/disease progression 375
– environmental stressors 372
– epidrugs 375
– factors 372
– gene expression 368
– genetic imprinting 371, 372
– histone modification 370
– immunology and periodontitis 373, 374
– modification 368, 369
– ncRNAs 370, 371
– OSCCs 374
– personalised medicine 374, 375
– phenotype 369
– post-translational modification 370
– role of 372
– tooth development 373
– transcription factors 369, 370
Erosion index 216
Ethics
– beneficence
  – biomedical research 416
  – compensation 416
  – confidentiality 415
  – economic risks 415, 416
  – equipoise 416
  – homosexuality 415
  – individual's participation 415
  – informed consent 416
  – IRBs and ethics committee 415
  – legal risks 415
  – pain, injury, and sensory impairment 415

Ethics (*cont.*)
– principle of 415
– psychological risks 415
– risks of participating 415
– social risks 415
– therapeutic misconception 416
– code of conduct for research
– Belmont report 411
– The Declaration of Helsinki 410, 411
– Nuremberg code 410
– IRBs/ethics committees 416
– justice
– benefits and risks 414, 415
– definition 413
– equity *vs.* equality 413
– potential participants 413, 414
– respect for individual
– autonomous agents 411
– clinical trials 412
– comprehension 412
– disclosure 412, 413
– research participants 411, 412
– voluntariness 412
Euchromatin 369
European Federation of Conservative Dentistry (EFCD) 210
European Organization for Research and Treatment of Cancer (EORTC) 199

F

Face rating scales (FRSs) 112
Faces pain scale (FPS) 112
Fallacies 285, 286
False negative rate (FNR) 488
False positive rate (FPR) 488
Falsification theory 268, 269
Fibromas 258
Fluorosis risk index (FRI) 128–129
Framingham health study 4
Functional teeth unit (FTU) 228

G

Gastrointestinal diseases 241
Geriatric/General Oral Health Assessment Index (GOHAI) 323
G-Formula 277
Gini coefficient 50, 51
Global Burden of Disease (GBD) study 224, 358
– age-standardized DALYs rates 26, 29
– age-standardized prevalence and incidence 26
– DALYs 24, 26, 28
– disability weight 24
– GATHER 25
– global age patterns 26
– global prevalence and incidence rate 28
– person trade-off 24
– prevalence and incidence 24
– severe periodontitis
– age-standardized DALYs rates 26, 32, 33
– age-standardized prevalence and incidence 26, 30
– CPITN score 30
– definition 30
– disability weight 30
– global age patterns 32
– global age-standardized prevalence 30
– population growth and ageing 32
– prevalence 26
– STROBE 25
– total tooth loss
– age-standardized DALYs rates 26, 30, 34
– age-standardized prevalence and incidence 26, 34
– definition 32
– global age patterns 34
– prevalence 26
– untreated dental caries
– age-standardized DALY rates 26, 29–32
– age-standardized prevalence and incidence 26, 29
– DALYs 30, 31
– disability weight 29
– DMFT index 29
– global age patterns 29
– initial stages 27
– pooled data analysis 29
– WHO criteria 27
– years lived with disability 24
– years of life lost 24
Global Cancer Observatory (GCO) 196
GLOBOCAN project 198
Gradient boosted trees 363
Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) 25

H

Halimeter™ scores 237, 238
Halitosis
– causes of
– airways 240
– bad breath formation 239, 240
– gastrointestinal diseases 241
– periodontal disease 240
– systemic diseases 241
– tongue coating 240
– transitory bad breath 241
– CTH-RJ 243, 244
– diagnosing-detecting bad breath
– accuracy 237
– BANA scores 237
– electronic nose 237
– Halimeter™ scores 237, 238
– organoleptic assessment 236, 238
– paradox 238
– VSC 236
– oral malodor 236
– prevalence 238, 239
– treatment
– anatomic deviations 243
– antibacterial local chemical products 242
– foods and medications 243
– local mechanical cleaning 242
– postnasal drip 243
– procedures 241
– psychological aspects 241, 242
– salivary stimulants/substitutes 242, 243
– systemic antibiotics 242
Hawthorne effect 390, 391
Health-related quality of life (HRQoL) 97
Health services research
– allocative efficiency 397
– behavioural model of health services 397, 398
– definition 396
– dental services

– applications of 403, 404
– changes in 402, 403
– classification 402
– linking services 404
– relative value units 403
– terms of access 402
– dental visits
– access to dental care 398
– check-up visits 400, 401
– demand/utilisation 401, 402
– family income 399
– favourable pattern 401
– independent variables 399
– inequality 399, 400
– number of visits 399
– predisposing variables 400
– problem-based visits 401
– socioeconomic demand 399
– time intervals 399
– process and outcome 397
– structure 397
– types 398
Heterochromatin 369
Higher education institutions (HEI) 454
Histone protein acetylation 368
Hopewood House study 4
Human immunodeficiency virus (HIV) 337
Hyperbilirubinaemia 171
Hyper-methylation 370
Hypo-methylation 370
Hypomineralised second primary molars (HSPM) 176

I

Index of Complexity Outcome and Need (ICON) 83
Index of Orthodontic Treatment Priority (Need) (IOTN) 81
Indirect path 273
Inductivism 268, 269
Institutional Review Boards (IRBs) 416
International Agency for Research on Cancer (IARC) 5
International Association for Research on Cancer (IARC) 196
International Association of Dental Traumatology (IADT) 134
International Caries Detection and Assessment System (ICDAS) index 43
International Head and Neck Cancer Epidemiology (INHANCE) 200
International Headache Society criteria (IHS) 109
International Perinatal Database of Typical Orofacial Clefts (IPDTOC) 160
Intersectionality theory 288
Intervention/experimental studies
– allocation criterion 16
– blind/masked allocation 17
– Cochrane systematic review 17
– community intervention 19
– CONSORT guidelines 17
– contamination 17
– demographic and clinical characteristics 16
– exposure effect 17
– intervention allocation criterion 16
– nutritional counselling 17
– quasi-experiment 16
– randomised studies 16
– RCT 17, 18
Intraclass Correlation Coefficient (ICC) 484, 485
Inverse-probability-of-treatment weights (IPW) 276

L

Latin American and Caribbean Health Sciences (LILACS) 217
Life course
– accumulation of risk models 297
– biological programming 296
– chains of risk 298
– critical and sensitive period models 297
– definition 296
– general and oral health 302, 303
– health inequalities 297
– intergenerational approach 303
– New Zealand Study–Dunedin 298, 299
– oral health influences 298
– Pelotas, Southern Brazil 299, 300
– predictive models 303, 304
– risk accumulation 296, 297
– socio-economic factors 301, 302
– sugar consumption and dental caries 303
Linear enamel hypoplasia (LEH) 176
Lorenz curve 51

M

Machine learning
– artificial intelligence 362
– artificial neural networks 363
– categorical variables 362
– example 362
– gradient boosted trees 363
– no-free-lunch theorem 363
– overfitting 362
– predictive models 362, 363
– random forests algorithm 363
– regression and classification problems 362
– sensitivity and specificity 362
– supervised learning 362
– types 362
Malocclusions
– ABO DI 81
– Ackermann & Proffit classification 81
– Andrew's six keys 81
– angle malocclusion classification 80
– anthropometric measurements 94
– child behaviour 94–96
– deciduous dentition 83–86
– Dewey's modification 80
– in epidemiological settings
– dental aesthetic index 83
– ICON 83
– IOTN 81
– PAR index 81
– main indices and criteria 82
– maternal characteristics 95, 96
– misaligned teet 80
– mixed dentition 87–89
– OHRQoL 80, 97–100
– permanent dentition 90–93
– preventable diseases and conditions 96, 97
– private practice/hospital-based clinical setting 80
– QoL 97, 99
– Simon's modification 81
– socioeconomic conditions 90, 94
Marginal structural modeling (MSM) 275, 276
Mean absolute error (MAE) 362

Measurement instruments
– clinical setting 467
– determinants of health conditions 466
– distribution of 466, 467
– frequency of 466
– observable phenomena 467
– OHRQoL 467
– selection of 467
  – construction and adaptation of scales 472–474
  – cross-cultural psychology 468
  – development stages 474–476
  – equivalent tools 468
  – quantitative studies 468
  – ready-to-use instruments 470, 472
  – recommendations 470, 471
  – relativism 468
  – research findings 467, 468
  – research scenarios 470
  – sociocultural factors 468
  – universalist perspective 468
– spectrum of intensity 467
Messenger RNA (mRNA) 368, 371
Metabolic syndrome (MetS) 303, 388
Methyl group 370
Methyl metabolism 372
Methylome 370
Micro RNAs (miRNAs) 374
Minimally important difference (MID) 324
Molar–incisor hypomineralisation (MIH) 171, 177–179, 183, 184
Multilevel regression models 288
Murray-Shaw index 126

N

National Child Oral Health Study (NCOHS) 123
National Dental Telephone Interview Surveys (NDTIS) 13
National Health and Nutrition Examination Surveys (NHANES) 45, 358
National Health Service (NHS) 350
Negative Predictive Value (NPV) 487
Neo-material theory 283
Net caries increment (NCI) method 42
New Zealand National Oral Health Survey 123
Non-coding ribonucleic acids (ncRNAs) 368, 370, 371
Nucleosomes 370
Nucleotides 370
Number needed to treat (NNT) 514
101-point numerical rating scale (NRS-101) 111

O

O'Sullivan's index 216, 217
Observational studies
– case-control studies 14, 15
– case reports or case series 10
– cohort studies 15, 16
– cross-sectional studies 12, 13
– descriptive studies 10
– ecological studies 10, 11
– time series studies 11, 12
Obstructive sleep apnea (OSA) 96
Odds ratio (OR) 514
Open/blocked path 273
Oral cancer
– analytic epidemiology
  – age and gender distribution 200
  – eating habits 201, 202
  – HPV 203, 204
  – INHANCE consortium 200
  – interaction and mediation 204
  – occupational risk factors 202
  – oral hygiene and dental status 202, 203
  – sociodemographic characteristics 201
  – tobacco smoking and alcohol drinking 200
– cancer registries 196
– cancer screening 205
– case fatality rate 196
– classification schemes 194
– codes for sites 195
– descriptive epidemiology
  – burden of disease 198
  – epidemiologic indices and social development 197
  – GLOBOCAN project 198
  – quality of life studies 199, 200
  – socioeconomic status 198
  – survival (or time-to-event) studies 198, 199
– epidemiological studies 194, 196, 197
– etiology 194
– European population 197
– incidence 195, 197
– morbidity indicators 196
– mortality rate 195, 197
– non-adjusted rates 197
– prevalence 195, 197
– proportional mortality ratio 195
– sex- and age-specific rates 197
– standard population distribution 198
– surveillance 196
– survival analysis 196
– treatment modalities 205
Oral health related quality of life (OHRQoL) 97–99, 224, 467
– applications 325, 326
– biomedical model 321
– biopsychosocial model 320–322
– chronic diseases 320
– conceptual framework 321
– European Court of Justice 320
– health utility and valued based healthcare 327
– health status measurement 321
– issues 326, 327
– measurement properties and key characteristics 323–325
– policy making level 327
– test of time 322, 323
Oral impacts on daily performances (OIDP) 322
Oral leucoplakia 374
Oral lichen planus (OLP) 374
Oral mucosal lesions (OML)
– data collection and analysis
  – clinical examination 252, 253
  – instruments of measurement 253, 254
  – limitations 254, 255
– definition 252
– molecular biology 259
– population-based studies 255, 258, 260
– prevalence
  – children and adolescents 255, 256
  – old people 257, 258
  – young and middle-aged adults 256, 257
Oral squamous cell carcinomas (OSCCs) 374
Organoleptic assessment 236
Orofacial pain
– aetiology of 108
– assessment of 108, 111
– burning mouth 109
– chronic and acute conditions 108

– chronic orofacial pain 108
– classification 110
– in clinical research 108
– definition 109
– dental pain and jaw pain 108, 115–118
– diagnosis and management 108, 109
– epidemiology of 112–115
– herpes simplex and aphthous stomatitis 108
– irreversible pulpitis 108
– management of 108
– odontogenic pain 109
– oral pain 108
– pain scales 111, 112
– with pathologic disorders 108
– pathophysiology 109
– in population-based studies 108
– prevalence of 109
– psychological factors 115
– quality of life 108
– socioeconomic factors 108
– Stedman's medical dictionary 109
– temporomandibular disorders 108, 109
– therapeutic modalities 108
– unidimensional and multidimensional pain scales 108
Oropharyngeal cancer 194

P

Peer assessment rating (PAR) index 81
Percentage of agreement (PA) 480, 481
Periodontal disease index (PDI) 60
Periodontal diseases 240
– age-specific prevalence 63
– analytical epidemiology 58
– behavioral factors 73
– CAL and PPD recordings 67
– calibrated examiners 67
– CDC-AAP classification system 67
– classification systems 58, 59
– clinical attachment loss 69
– continuum of disease severity 63
– country/region 73
– cross-sectional studies 68, 71
– cumulative distribution graphs 63
– cumulative frequency distributions 63, 64
– definition 58
– demographic characteristics 58
– descriptive epidemiology 58
– descriptive periodontal epidemiology 70, 71
– distribution of gingival disease 60
– epidemiological features 74
– epidemiological findings 58
– epidemiological studies 62, 63
– gingivitis and periodontitis
  – age 71, 72
  – aggressive and chronic periodontitis 59
  – biological disadvantage 60
  – BOP score 61
  – causal factors 59
  – clinical attachment loss 59, 62
  – clinical data 61
  – composite indices 61
  – composite recording methods 61
  – compound causes 59
  – CPI 61
  – definition 60
  – diagnostic tools 62
  – direct CAL measurements 62
  – dogmas 61
  – gender 72
  – gingival indices 61
  – indirect method for CAL estimation 62
  – nominalistic 59
  – oral hygiene practices 60
  – partial recording protocol 61, 62
  – pathological deepening of periodontal pocket 62
  – PDI 60
  – plaque-induced gingivitis 59
  – pristine clinical health 60
  – probing pocket depth 62
  – radiographic bone levels 62
  – recession 62
  – Russell periodontal index 60
  – severe-disease-for-age yardstick 60
– methodological issues 67
– mild-moderate periodontitis 73
– operational diagnostic criteria 59
– partial recording protocol 68
– periodontal recordings 62, 70
– prevalence 68
– race/ethnicity 72
– recording protocols 67
– reporting standard 65, 66
– severity 62
– socioeconomic factors 73
– study of distribution 58
– tooth loss difference 68
– tooth retention rates 68, 70
– valid inference 68
– variation in disease occurrence 58
– within-population variation 58
Periodontitis
– admission rate 391
– allocation bias 391
– attrition rates 391
– blinding 391
– collider variable 383
– compliance bias 391
– conceptual model 381
– confounding 382
– diabetes
  – bidirectional association 389
  – hyperglycemia 389
  – neutrophils 389
  – observational and interventional designs 390
  – proinflammatory cytokines 389
  – RCTs 389, 390
– Hawthorne effect 390, 391
– mediation 382
– misclassification bias 391
– plausibility 381
  – APO 387
  – CVD 385–387
  – direct mechanism 385
  – indirect mechanism 385
  – MetS 388
  – obesity 388
  – onset and progression 387, 388
  – proinflammatory mediators 385
  – systemic effects 385
  – theories 384, 385
– sample sizes 391
– smoking 383, 384
– temporality 381, 382
Perry Preschool Project (PPP) 428
Pilocarpine 242

Politics
– cholera, typhoid fever and yellow fever 422
– critical reflection 421, 422
– dental public health 423–425
– digital media 420
– examples 422
– feudalism 421
– functions for 420, 421
– health-illness process 421
– inequalities 425, 426
– information society 420
– interpretation of societies 421
– knowledge 420
– logical empiricism 421
– new public health 422, 423
– oral health 426
  – economics 425
  – factors 426, 427
  – inverse equity hypothesis 430
  – mechanisms 425
  – Medicaid policies 431
  – policy debate 429
  – political decisions 425
  – political institutions 425
  – population 425, 426
  – population health 427–429
  – priorities set 425
  – psychosocial factors 425
  – public funding and universal coverage 430
  – public policy 429
  – safety and effectiveness 430, 431
  – services and initiatives 429
  – social organization 425
  – sugary foods and drinks consumption 431
  – universal coverage and primary care approach 429
  – water fluoridation 430
– political force 422
– population 421
– and power relations 421
– practice of indifference 422
– public/state policies 420
– social conscience 420
Positive predictive value (PPV) 487
Potential outcome approach 288, 289
Primary care 350
– advantages and disadvantages
  – practice level data 351
  – routinely reported data 350, 351
– BSA 350
– connected and wearable devices 354
– data collection 349, 350
– data element 350
– dental epidemiology 348, 349
– external clinical/non-clinical staff 352, 353
– health service model 350
– hypothesis generating 354
– NHS 350
– settings 349
– technological approaches 353, 354
– workforce 350, 352
Probabilistic causation 270, 271
Public Health Dentistry 340, 424
Public opinion 129
Pulpal involvement, Ulceration, Fistula, and Abscess (PUFA) index 43

Q

Quality assurance (QA) 461
Quantitative bias analysis
– bias parameters 497
  – external data 500
  – forms of 498
  – internal data 500
  – measurement error 500
  – misclassification 499, 500
  – selection bias 498, 499
  – systematic error 497
  – tooth decay and impaired sleeping 500–502
  – unmeasured confounding 499
– estimated parameter 496
– point estimate 497
– policy decisions 497
– results 502, 503
– sample size and power computations 497

R

Random forests algorithm 363
Randomized clinical trials (RCTs) 382, 389, 390
Receiver operating characteristic curve (ROC) curve 489–491
Relative risk (RR) 514
Reliability coefficient (R) 484, 485
Reproducibility of results
– Kappa statistics
  – classification scales 481
  – contingency table 481
  – Dice index 485, 486
  – examiners' data 481
  – ICC 484, 485
  – nominal data 481
  – programs 481
  – reproducibility studies 482, 483
  – weighted Kappa 481
– laboratory, clinical/epidemiological conditions 480
– measurement of 480
– percentage of agreement 480, 481
– performance of 492
– validity evaluation
  – Bayes' theorem 490–492
  – contingency table 487
  – correct classification 488
  – development of 486
  – dichotomous outcomes 486
  – DOR 488
  – examination outcomes 486
  – FNR 488
  – FPR 488
  – gold standard method 486
  – likelihood ratios 487, 488
  – NPV 487
  – PPV 487
  – ROC curve 489–491
  – sensitivity and specificity 487
  – signs and symptoms 486
  – statistical computing 487
  – Youden's J Statistic 488
Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) 109
Root caries 41
Russell periodontal index (PI) 60

S

Salivary gland neoplasms 258
Scopus, Scientific Electronic Library Online (SciELO) 217
Selection bias 273
Severe tooth loss 224, 226–228
Short form (SF) 325
Significant caries index (SiC) 49
Sjogren syndrome 242
Social determinants of health 337
Socio-economic inequality
– Black report
  – artefact 282
  – behavioural/cultural explanations 282, 283
  – materialist/structuralist explanations 282, 283
  – neo-material theory 283
  – psychosocial explanations 283
  – social capital 283
  – theories of natural/social selection 282
– causal inference 288, 289
– decomposition 289
– disadvantage 280
– intersectionality theory 288
– measurement
  – analysis 286
  – composite measures 286, 287
  – fallacies 285, 286
  – scale of 287, 288
  – types 284, 285
  – variations 285
– motivations 281, 282
– operationalisation 284
– potential outcome approach 288, 289
– randomized controlled trials 280
– simulation modelling 289
Socio-economic position (SEP) 297
Soft tissues, *see* Oral mucosal lesions (OML)
Square root of the mean squared error (RMSE) 362
Statistical association 271, 272
Statistical inference 268
Strengthening the Reporting of Observational Studies (STROBE) 25
Structural equation modeling (SEM) 276, 303
Sufficient-component model 269, 270
Sugar consumption
– free sugars
  – CVD 311
  – dental caries 309, 310
  – diabetes 311
  – dried fruit 310
  – frequency/amount of 310
  – milk sugar 310
  – periodontal disease 310
  – unhealthy weight gain 310, 311
  – world sugar production 311–313
– life course 303
– power imbalance 308
– prevalence 308
– reduction 314, 315
– social and commercial determinants 313, 314
– WHO classification 308, 309
Sugar-sweetened beverages (SSB) 310
Supervised learning 362
Survey of Health, Ageing and Retirement in Europe (SHARE) 358
Systematic reviews
– characteristics 508, 509
– data collection process
  – data extraction bias 513
  – observational studies 513
  – publication and identification bias 511, 512
  – quality evaluation 512, 513
  – randomized controlled trials 511
  – results 511
  – selection of studies 512
– definition 508
– guidelines 511
– health economics 520
– implementation research 520, 521
– locating, evaluating, and synthesizing evidence 508
– meta-analysis 509
  – characteristics 514
  – clinical trials 520
  – fixed effects model 515, 516
  – forest plot 515
  – heterogeneity 516, 517
  – homogeneity tests 518
  – intervention and outcome 514
  – network-meta-analysis 518, 519
  – publication bias 517, 518
  – random effects model 516
  – randomized trial 514
  – robustness 517
  – standardized difference of means 515
  – vote counting 514
  – weighted average 515
  – weighted difference of means 514
– *vs.* narrative reviews 508, 509
– observational studies 509, 510
– pooling studies 511
– principles 511
– resources 510, 511
Systemic diseases, *see* Periodontitis

T

Teaching methods
– assessment methods 459–461
– course documentation
  – course/study guide 454, 455
  – and learning methods 456–458
  – learning objectives 455, 456
– curriculum 458, 459
– quality assurance 461
– regulation 454, 455
Teledentistry 260
Temporomandibular disorders 108
Thylstrup & Fejerskov (TF) index 127
Tooth loss
– categorizations of remaining teeth 228
– DALYs 224
– dental examination 226
– disease burden 226, 227
– incidence 224, 225
– masticatory function 224
– number of natural and artificial teeth 225, 226
– number of remaining teeth, Japanese population 225
– prevalence 224, 225
– risk factors/predictors for 228
  – distal factors for 230
  – intermediate factors for 228–230
  – proximal factors for 228, 229
– self-reported measurements 226–228

Tooth surface index of fluorosis (TSIF) 128, 129
Tooth wear index (TWI) 215
Transitory bad breath 241
Traumatic dental injuries (TDI)
– associated factors 137
– classification and definition 134, 135
– contextual and individual variables 145
– core outcome set 135
– demineralization-remineralization process 134
– effect measures 138
– effect on permanent successor 137
– epidemiological studies 134
– etiology 137
– evidence-based prevention and treatment strategies 135
– generic outcomes 135
– incidence 136
– infection-related resorption 136
– medium-term and long-term treatment 134
– observational designs 135
– OHRQoL 134
– in permanent teeth
  – associated factors 144
  – behavioral variables 147, 148
  – contextual variables 144, 145
  – demographic factors 146
  – OHRQoL 150, 151
  – oral factors 148, 149
  – prevalence and distribution 140–143
  – psychological and social variables 147
  – risk factors 144
  – socioeconomic factors 146, 147
– prevalence 134–136
– primary prevention 152
– in primary teeth
  – associated factors 144
  – behavioral variables 147, 148
  – contextual variables 144, 145
  – demographic factors 146
  – OHRQoL 149, 150
  – oral factors 148, 149
  – prevalence and distribution 138–140
  – psychological and social variables 147
  – risk factors 144
  – socioeconomic factors 146, 147
– p-value measures 137
– RCTs 135
– repair-related resorption 136
– risk factors 134, 138
– secondary and tertiary prevention 152, 153
– study designs and frequency measures 135
– teachers role 151
– tooth fractures 137
– treatment and prognosis 152–153

U

Union for International Cancer Control (UICC) 197
Universal Health Coverage (UHC) 430

V

4-point verbal rating scale (VRS-4) 112
5-point verbal rating scale (VRS-5) 112
Vipeholm study 4
Virtual learning environment (VLE) 455
Visual analogue scale (VAS) 111
Volatile sulfur compounds (VSC) 236

W

Water fluoridation
– caries outcomes
  – incidence of 449
  – increment of 449
  – intra-oral distribution 447, 448
  – national oral health surveys 448
  – natural history 447, 448
  – overview 446, 447
  – summed score 448
– clinical findings 440, 441
– evolution of 438–440
– exposure
  – adults and older adults 445, 446
  – community trials 444
  – concurrent controls 444, 445
  – individual-level 443, 444
  – induction period 443
  – outcome 443
  – population-level 443, 444
– heterogeneity 441
– observer bias 442, 443
– risk of bias 441, 442
– study design 442
Wong-Baker Faces Scale 112

Y

Years lived with disability (YLD) 226, 227

Z

Zero-inflated Poisson model 52