Respiratory Medicine
Series Editor: Sharon I.S. Rounds

Lynn B. Gerald
Cristine E. Berry *Editors*

Health Disparities in Respiratory Medicine

ATS
We help the world breathe®
PULMONARY • CRITICAL CARE • SLEEP

Humana Press

Respiratory Medicine

Series Editor:
Sharon I.S. Rounds

More information about this series at http://www.springer.com/series/7665

Lynn B. Gerald • Cristine E. Berry
Editors

Health Disparities in Respiratory Medicine

Humana Press

We help the world breathe®
PULMONARY • CRITICAL CARE • SLEEP

Editors
Lynn B. Gerald, PhD, MSPH
Arizona Respiratory Center and Department of Health Promotion Sciences
Mel and Enid Zuckerman College of Public Health
University of Arizona
Tucson, AZ, USA

Cristine E. Berry, MD, MHS
Arizona Respiratory Center and Department of Medicine, Division of Pulmonary
Allergy, Critical Care and Sleep Medicine
College of Medicine
University of Arizona
Tucson, AZ, USA

ISSN 2197-7372 ISSN 2197-7380 (electronic)
Respiratory Medicine
ISBN 978-3-319-23674-2 ISBN 978-3-319-23675-9 (eBook)
DOI 10.1007/978-3-319-23675-9

Library of Congress Control Number: 2015947791

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Humana Press is a brand of Springer
Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Contents

Contributors

Christian Bime, M.D., M.Sc. Department of Medicine, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, College of Medicine, University of Arizona, Tucson, AZ, USA

Sonali Bose, M.D., M.P.H. Division of Pulmonary and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, MD, USA

Kelly J. Brunst, Ph.D. Department of Pediatrics, Kravis Children's Hospital at Mount Sinai, New York, NY, USA

Jennifer Cabe, M.A. Canyon Ranch Institute, Tucson, AZ, USA

Richard H. Carmona, M.D., M.P.H., F.A.C.S. Canyon Ranch Institute, Tucson, AZ, USA

Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

Nancy Gonzalez Casanova, M.D., M.P.H. Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, Tucson, AZ, USA

Juan C. Celedón Division of Pulmonary, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA, USA

Scott Cerreta The COPD Foundation, Washington, DC, USA

Ching-Fei Chang, M.D. Division of Pulmonary, Critical Care, and Sleep Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

Daniel Monroy Chaves, M.D. Division of Pulmonary, Critical Care, and Sleep Medicine, The MetroHealth Campus of Case Western Reserve University, Cleveland, OH, USA

J. Randall Curtis, M.D., M.P.H. Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, WA, USA

Gregory B. Diette, M.D., M.H.S. Division of Pulmonary and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, MD, USA

Gary Ewart American Thoracic Society, Washington, DC, USA

Pebbles Fagan, Ph.D., M.P.H. Cancer Prevention and Control Program, University of Hawaii Cancer Center, University of Hawaii at Manoa, Honolulu, HI, USA

Gary S. Feigenbaum, M.D. Department of Internal Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

Patricia W. Finn Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

Joe G.N. Garcia, M.D. Senior Vice President for Health Sciences, Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, Drachman Hall, Tucson, AZ, USA

Rachele A. Gibson, M.D. Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Michael K. Gould, M.D., M.S. Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA

Meghan Halley, Ph.D., M.P.H. Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA

Louise Hecker, Ph.D. University of Arizona, Southern Arizona VA Health Care System, Department of Medicine, Tucson, AZ, USA

Sarah Knowles, Ph.D., M.P.H. Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA

Jerry A. Krishnan Breathe Chicago Center, Division of Pulmonary, Critical Care, Sleep and Allergy, University of Illinois in Chicago, Chicago, IL, USA

Jamie Lamson-Sullivan The COPD Foundation, Washington, DC, USA

Ann C. Long, M.D., M.S. Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, WA, USA

Jose S. Loredo, M.D., M.S., M.P.H. Department of Medicine, University of California San Diego School of Medicine, San Diego, CA, USA

David M. Mannino, M.D. Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, Lexington, KY, USA

Sarah A. Narotzky, M.D. Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Jorge R. Navarrete, M.D. Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, Tucson, AZ, USA

Eyal Oren, Ph.D., M.S. Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

Andrew Pleasant, Ph.D. Canyon Ranch Institute, Tucson, AZ, USA

Hector Quijada, B.S. Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, Tucson, AZ, USA

Kenneth D. Rosenman, M.D. Department of Medicine, Michigan State University, East Lansing, MI, USA

Paul D. Scanlon, M.D. Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Miriam Siegel Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, Lexington, KY, USA

Joseph H. Skalski, M.D. Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

John Daryl Thornton, M.D., M.P.H. Division of Pulmonary, Critical Care, and Sleep Medicine and Center for Reducing Health Disparities, The MetroHealth Campus of Case Western Reserve University, Cleveland, OH, USA

Sandra R. Wilson, Ph.D. Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA

Rosalind J. Wright, M.D., M.P.H. Department of Pediatrics, Kravis Children's Hospital at Mount Sinai, New York, NY, USA

Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Hemang Yadav, M.B.B.S. Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

The original version of this book was revised. An erratum to this book can be found at DOI 10.1007/978-3-319-23675-9_17

Chapter 1
Introduction to Health Disparities and Respiratory Health

Andrew Pleasant, Jennifer Cabe, and Richard H. Carmona

A review of a 2014 report released by the Forum of International Respiratory Societies makes the case for an increased focus on respiratory health crystal clear, "the morbidity and mortality related to lung diseases is staggering. Hundreds of millions of people are burdened with chronic respiratory conditions; four million people die prematurely from chronic respiratory diseases each year. Respiratory infections are the leading cause of death in developing countries [1]."

Most respiratory illnesses are avoidable. The cost of prevention—as is the case with most chronic disease—is only a fraction of the cost of treatment. While research is always important, we very often already know how to prevent the millions of cases of chronic respiratory illness occurring around the world [2].

We hold a high value for basic research, but perhaps nowhere more than in this arena is there a critically important need for applied research and informed advocacy.

The leading respiratory diseases—where the most gain is likely—are chronic obstructive pulmonary disease (COPD), asthma, acute respiratory infections, tuberculosis, and lung cancer. The most fruitful areas for solutions are also very well known and researched: the use of tobacco, indoor and outdoor air quality, childhood immunizations, nutrition, and physical activity/exercise.

As is well demonstrated throughout this volume, access to better living conditions, escape from poverty and unhealthy environments, and having hope for tomorrow

A. Pleasant, Ph.D. (✉) • J. Cabe, M.A.
Canyon Ranch Institute, Tucson, AZ, USA
e-mail: andrew@canyonranchinstitute.org

R.H. Carmona, M.D., M.P.H., F.A.C.S.
Canyon Ranch Institute, Tucson, AZ, USA

Mel and Enid Zuckerman College of Public Health,
University of Arizona, Tucson, AZ, USA
e-mail: rcarmona@canyonranch.com

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_1

are often least available to those who would benefit the most. These structural determinants of health are not a mystery—we currently have the knowledge of how to improve those. What the world lacks is the will. Our hope, and thus we are collaborating on this introduction, is that collections of evidence and understanding such as this volume will help create that will.

In this volume, you will explore complex connections between poor respiratory health, the proximal causes, the social and environmental determinants that underpin those causes, and suggested solutions.

Following this introduction, in the remainder of this volume you can explore the creation and possible responses to health disparities in regard to tobacco smoke exposure, environmental air quality, occupational exposures, pulmonary function testing, medication adherence, acute respiratory distress syndrome (ARDS), asthma, COPD, tuberculosis, lung cancer, critical illness, sleep-related breathing disorders, and end-of-life care.

First, Fagan offers insight into disparities associated with exposure to tobacco smoke. Fagan writes, "Tobacco affects nearly every organ in the body [3] … Annual indirect costs due to productivity losses are $150 billion [4] and medical expenses range from $130 billion to $176 billion [4]."

Fagan accurately points out and relies on the history of reports on tobacco from the U.S. Surgeons General—beginning with the first report now over 50 years ago by Surgeon General Dr. Luther Terry. These reports have driven not only more scientific research and significant changes in policy around the world but also helped improve health literacy so people are better equipped to find, understand, evaluate, communicate, and use information to make informed choices and change behaviors in relation to their health and well-being [5, 6].

In Chap. 3, Bose and Diette take on issues of health disparities related to environmental air quality. The pair explores disparities related to socioeconomic status, race, gender, age, and place. While maintaining awareness that certain groups—people in poverty, racial minorities, women, children, the elderly, those living in developing rural areas, and inner-city residents—face an unfair burden of the adverse effects, they also remain aware that "no one group can be 'safe' or immune to the far-reaching nature of outdoor pollution as it sweeps across continents, nor to the toxins emerging from the indoor environments that we create in our own homes in which we purposefully seal ourselves."

Chapter 4 takes a look at occupational exposures with a series of brief case studies on issues such as chromates, coke oven emissions, cotton dust in textile mills, Navajo miners in uranium mines, rubber workers, exposure to silica in drilling and mining, and work-related asthma. The chapter's author, Rosenman, calls for improvements in monitoring systems, including, "requiring the reporting of race in the annual Bureau of Labor Statistics employer based survey on injuries and illnesses; adding race as a core variable in worker compensation state data systems; adding industry and occupation to the core module of the annual BRFSS survey administered in the 50 states; and routinely collecting information about occupation/employer in medical records and making collection of such information a

requirement for future meaningful use incentives as part of the transition to electronic medical health records."

In Chap. 5, readers will explore health disparities in the context of pulmonary function testing. Skalski, Gibson, Narotzky, Yadav, and Scanlon explore disparities related to access, language barriers, cultural variations among English speakers, reference values for pulmonary function testing based on gender, age, height, and ethnicity, and corrections based on self-reported race.

The authors of this chapter explore, in part, the two-sided nature of many underpinning causes of health disparities—the failure of health care professionals and systems to effectively communicate as well as the level of skills and abilities in many of the populations they serve. In this context, the authors argue that "an important aspect of lung function testing is that accurate testing is highly dependent on patient performance." While avoiding blaming the victims, the authors conclude that "all of this makes PFTs more sensitive than many other medical diagnostic tests to linguistic and cultural barriers that may exist between testing personnel and the patient. Furthermore, for a patient to have access to accurate PFTs, they must not only have access to a medical facility with equipment and willingness to perform the PFTs but they must also have appropriately trained technicians at that facility, assisted by translators when necessary, to perform maximal and error-free tests."

In Chap. 6, Wilson, Halley, and Knowles explore health disparities as they relate to medication adherence. They begin their focus by discussing disparities related to characteristics of the health care delivery system, the physician/patient relationship, disease and treatment regimen, and characteristics of the patient—such as age, gender, health literacy, income, insurance, socioeconomic status, comorbidities, and race and ethnicity.

As is true of discussions of disparities in general, medication adherence studies often blame, or verge on blaming, the patients and even more frequently focus on whether, not how, the medications were taken, while neglecting the demand side of the equation coming from the health care system. That history is reflected in this review of the literature to date in Chap. 6. Reflecting the state of disparities research overall—which is the driver of the content of this book—the authors of this chapter call for better measurement, better theory, and more equitable and practical research and practice. We couldn't agree more, but do suggest the argument can be taken further in terms of the causative factors related to social determinants of health such as health literacy, a focus on prevention versus documenting effects, and an even stronger emphasis on identifying causes within the sick care system—the demand side—versus placing such an emphasis on patients.

The next chapter shifts the focus to health care disparities in ARDS. Briefly stated, ARDS is a life-threatening lung condition that prevents enough oxygen from getting to the lungs and the blood. Casanova, Navarrete, Quijada, Hecker, and Garcia highlight that further ARDS research studies focused on Latinos, African Americans, Native Americans, and other minorities are needed to understand the multifactorial causes associated with disparities. They conclude by pointing out the

potential benefits from increased and continued studies focused on genomic and epigenetic analysis of the risk factors underlying ARDS.

Chapter 8, written by Brunst and Wright, takes a look at the role of social stress in asthma disparities. They suggest, "Social toxicity experienced as increased psychological stress is likely a major driver of observed disparities in lung growth and development and asthma, as well as a range of other respiratory conditions. Most respiratory conditions likely share overlapping etiology; therefore, multiple mechanistic pathways with complex interdependencies must be considered when examining the integrative influence of stress independently as well as the interaction of social and physical environmental toxins in explaining the social patterning of respiratory diseases. Because these factors tend to cluster in the most socially disadvantaged, this line of research may better inform the etiology of growing health disparities increasingly documented for respiratory disorders."

While we don't disagree, we wonder if solutions to disparities might also be discovered by looking at where they don't exist, as well as where they do. Communities and individuals suffering greater prevalence of disease are certainly where researchers will identify disparities and their associations, but observing where disease is not prevalent may be a better way to understand what changes need to be put in place to prevent disparities from occurring at all.

Bime continues the focus on asthma by looking at disparities related to patient factors, social and environmental factors, and factors related to health care systems and health care professionals. Asthma is perhaps the quintessential example of health disparities. Bime describes that situation very well and concludes with a call for greater emphasis on "adequate representation of members of high-risk populations and minority investigators that should be involved in the research."

The next chapter by Siegel, Krishnan, Lamson-Sullivan, Cerreta, and Mannino focuses on health disparities in chronic obstructive pulmonary disease (COPD). The authors point out the multitude of types of disparities in COPD that currently exist—from death rates and frequency in various populations to perception of the disease. They discuss disparities related to race and ethnicity, gender, age, genetic predisposition, geographic residence and location of care, type of chronic illness, un- and under-insured, work trajectory and unemployment, income inequality, and the nature of critical care settings.

In Chap. 11, health disparities and tuberculosis (TB) become the central point of interest. Oren argues that "as with many other diseases, the TB burden follows a clear socioeconomic gradient, with the poorest at the most elevated risk." For example, Oren reports that "worldwide, one out of three persons is infected with M. tuberculosis, with 1.5 million deaths due to TB… In the U.S.A., foreign-born persons have case rates 11.5 times higher than U.S. -born persons, and among the U.S. -born, the largest disparities are between blacks and whites; where TB rates in blacks are 5.8 times greater than among whites, and distribution is geographically heterogeneous, with California, Texas, New York, and Florida reporting half of all TB cases in 2012."

A true highlight of this volume is Chap. 12 by Chang, Feigenbaum, and Gould that takes a definitive look at disparities in lung cancer outcomes. Taking a proactive

view and offering a series of practical and tangible recommendations to address the issue, the authors set up the problem by arguing that "despite good intentions and the passage of major legislation, significant social, economic, and cultural barriers still persist that undermine access to appropriate health care for those at greatest risk for lung cancer. Thus social revolution, rather than technological innovation, may be the true answer to improving lung cancer mortality in America on a large scale."

Taking a broad and holistic approach, Chang, Feigenbaum, and Gould assert that "no matter what kind of modern miracles medicine may offer, the social paradigms in America will ultimately define what kind of impact they achieve in regard to lung cancer outcomes." They suggest aggressive action to address tobacco prevention, improvement of infrastructure and environments within poverty-stricken communities, universal health care, standardization of practices within health care, health care professionals receiving training in cultural sensitivity, increased enrollment of underrepresented populations in clinical trials, and a new appreciation of "the complexity of lung cancer biology, including gender differences and genetic mutations, leading to more targeted, effective, and personalized therapy."

Health disparities in critical illness are the focus of the Chap. 13, offered by Chaves and Thornton. As is true for much of this volume, this chapter paints a detailed picture of the issue. The authors sum up the issue, accurately, by stating, Race and ethnicity also continue to be used as poor substitutes for the true factors that need to be identified including income, insurance status, location where healthcare was delivered, neighborhood of residence, and work trajectory. This not only leads to false declarations, but it prevents the field from moving forward as it implies that such factors and their associated outcomes are not modifiable.

Loredo offers in Chap. 14 a focus on health disparities in sleep-related breathing disorders. For those looking for an in-depth introduction to the existing science of sleep and sleep-related breathing issues, go no further. The case is made that while the importance of sleep to health has only been recently recognized, the nature, causes, and extent of disparities in sleep and sleep-related breathing disorders are areas where more research is needed.

Health disparities in end-of-life care are the focus of Long and Curtis in Chap. 15. The authors explore differences in end-of-life care across patient characteristics, including gender; race and ethnicity; socioeconomic status; health literacy; and members of the lesbian, gay, bisexual, and transgender community. It seems more work may be needed to fully explore the extent of causes of disparities in this area that may reflect the health care system and/or the patient and their family's responses to end-of-life issues. The authors conclude, "Cultural competence in end-of-life care must be a priority for health care providers in order to improve communication for nonwhite patients and their family members and ensure respect for informed decisions that reflect patient and family preferences."

Wrapping up this volume focusing on health disparities and respiratory health issues, Celedón, Ewart, and Finn offer a chapter titled, "Where do we go from here? Improving disparities in respiratory health." The authors base their argument on the all-too-well-known but under-addressed reality that "current health disparities are not only morally unacceptable but financially unsound."

Causing that unwise and unsound approach is a lack of prevention of respiratory health issues. The authors acknowledge that the modifiable risk factors for most respiratory health issues are environmental and lifestyle risk factors—tobacco use, air pollution, and occupation—and that those determinants are unevenly distributed in society. To conclude, the authors call for true universal health care, more research, a more diverse health care workforce, environmental justice, healthier lifestyles, and advocacy.

There are two important issues, in our view however, that deserve further attention than they receive in the volume that follows. One is the importance of health literacy as a solution. The second is a need for the scientific enterprise to begin not only to embrace calls for more research but also to propose functional solutions and responses to the social determinants of health.

Health literacy is being shown to be one of the strongest social determinants. While the concept is mentioned in some—but far from all—of the chapters in this volume, the idea is worthy of greater consideration in the realm of health disparities. Respiratory illnesses may prove a key context in which to fully deploy the ability of health literacy not as a diagnosis, but as a powerful tool of prevention. One issue this volume, in its totality, makes perfectly clear is that in order to prevent and treat respiratory illnesses, true partnerships must occur between health care professionals and the individuals and communities they are striving to serve.

In this age, when we face shortages in qualified health care professionals, the burden of addressing chronic diseases of all types will only succeed through forging new partnerships between the public and the health care systems based on the best practices of health literacy. Only then we can successfully transform our current sick care systems into true health care systems focusing on prevention. The benefits of that transition will be significant to all of the global community.

Finally, we close with a plea to all readers. Research is incredibly valuable—but not when it sits on a dusty shelf for years before it is utilized. We fully embrace the need for verification and building a body of evidence, but such a vast majority of book chapters and journal articles simply conclude with a call for further research that it is no wonder society does not give due heed to the lessons learned through vigorous and reliable research. We hope that researchers will conclude with a call to action and advocate for application of their findings. Furthermore, we hope that readers will be inspired to implement evidence-based solutions derived from such research.

Certainly, part of the know-do gap—the gap between what people know and what they actually do to improve or maintain their health—has many explanations and causes. We hope that the exceptional discussions in this text of the complex scientific and social issues around pulmonary disease will inspire all of us to aggressively translate what we know into effective and sustainable public health programs that reduce morbidity, mortality, and cost while improving the quality of life for our fellow citizens.

References

1. Ferkol T, Schraufnagel D. The global burden of respiratory disease. Ann Am Thorac Soc. 2014;11(3):404–6. doi:10.1513/AnnalsATS.201311-405PS.
2. Respiratory diseases in the world: realities of today—opportunities for tomorrow: Forum of International Respiratory Societies. 2014.
3. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the surgeon general. Atlanta, GA: U.S. Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2004; Washington, D.C.: For sale by the Supt. of Docs., U.S. G.P.O.
4. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the surgeon general. Atlanta: U.S. Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2014.
5. Coleman C, Kurtz-Rossi S, McKinney J, Pleasant A, Rootman I, Shohet L. Calgary charter on health literacy. 2009. http://www.centreforliteracy.qc.ca/Healthlitinst/Calgary_Charter.htm. Accessed 13 July 2015.
6. Zarcadoolas C, Pleasant A, Greer D. Understanding health literacy: an expanded model. Health Promot Int. 2005;20:195–203.

Chapter 2
Health Disparities in Tobacco Smoking and Smoke Exposure

Pebbles Fagan

Key Points

- While overall smoking rates have decreased in the USA, disparities related to tobacco smoking by race/ethnicity and socioeconomic status persist.
- Secondhand smoke exposure also differs by race/ethnicity and socioeconomic status, but objective measurement using cotinine levels is complex because nicotine metabolism differs by gender, race/ethnicity, and type of cigarette consumed.
- Reporting aggregate data on racial/ethnic groups, sampling strategies that capture small numbers of disparate groups, and low response rates to national surveys are examples of some of the methodological challenges that influence the study of tobacco-related health disparities.
- Comprehensive tobacco control programs are essential in developing strategies to reduce health disparities in tobacco-related respiratory diseases.

Introduction

Cigarette smoking rates in the USA have dramatically declined in the past 50 years, and the reduction in cigarette smoking is one of the top public health achievements in the 20th and 21st centuries [1, 2]. Per capita cigarette consumption has declined from 4345 cigarettes in 1963 to 1196 cigarettes in 2012 [2]. However, in the past 10 years, declines in cigarette smoking have slowed among adults [3].

P. Fagan, Ph.D., M.P.H. (✉)
Cancer Prevention and Control Program, University of Hawaii Cancer Center, University of Hawaii at Manoa, 701 Ilalo Street, Honolulu, HI 96813, USA
e-mail: pfagan@cc.hawaii.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_2

Approximately 42 million Americans smoke, putting many smokers at risk for tobacco-related and -caused diseases and conditions [4].

Tobacco exposure, including cigarette smoking and secondhand smoke exposure (SHS), is the leading cause of preventable death in the USA [5] and globally [6]. Worldwide, tobacco kills more than six million people annually and in the USA, an estimated 480,000 Americans die each year from tobacco exposure [2]. Cigarette smoking is responsible for one in five deaths in the USA annually [2]. Since 1964, 20 million Americans have died from smoking-attributable diseases [2]. Tobacco affects nearly every organ in the body [7]. Tobacco exposure in utero and among children, adolescents, and adults can increase the risk for adverse reproductive health outcomes, cancer, cardiovascular disease, respiratory disease, hip fractures, sudden infant death syndrome, cataracts, and other conditions [7] (see Table 2.1). There are economic costs as well. Annual indirect costs due to productivity losses are $150 billion [2] and medical expenses range from $130 billion to $176 billion [2].

There are 16 million people in the USA who have at least one tobacco-related serious illness [2], and tobacco is associated with the top three leading causes of death in the USA. Among adults age 35 years and older, 41 % of all smoking attributable deaths are due to cancer [7], 32.7 % are due to cardiovascular disease, and 26.3 % are due to respiratory disease [8]. The three major categories of tobacco-caused deaths are lung cancer ($n = 128{,}922$), ischemic heart disease ($n = 126{,}005$), and chronic obstructive pulmonary disease (COPD) ($n = 92{,}915$). In addition, 49,400 lung- and heart disease-related deaths are due to SHS annually [8].

About 90 % of all lung cancers in the USA are due to tobacco [8], and lung cancer is the leading cause of cancer mortality in the USA. From 2005 to 2011, 5-year survival rates have increased from 11.4 to 17.4 %, but survival rates remain quite low [9]. Lung cancer comprises an estimated 13.3 % of all new cancers and 26.8 % of cancer deaths [9]. Most importantly, lung cancer can nearly be eliminated if tobacco were eliminated. Therefore, the prevention of lung cancer by targeting tobacco exposure has been a primary goal for the U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion [10]. Unfortunately, tobacco-caused respiratory diseases and conditions other than lung cancer have received less attention. Tobacco exposure affects the trachea, bronchi, and the lungs. The primary nonmalignant respiratory diseases caused by tobacco exposure are asthma and COPD, which includes emphysema and chronic bronchitis.

The 1964 Surgeon General's report, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*, was the first document to conclusively state that smoking causes chronic bronchitis [11].

"Cigarette smoking is the most important cause of chronic bronchitis in the USA and increases the risk of dying from chronic bronchitis [11]."

The casual relationship between smoking and COPD was later confirmed in the 1984 Surgeon General's report, *The Health Consequences of Smoking: Smoking and Chronic Obstructive LungDisease* [12]. Subsequent reports further supported this finding, and additional diseases and conditions have been causally linked to

Table 2.1 Diseases and conditions causally linked to tobacco exposure

Cancer	Cardiovascular	Respiratory	Other
• Oropharynx	• Stroke	• Chronic obstructive pulmonary	• Oral clefts[a]
• Larynx	• Coronary heart disease	• α1-antitrypsin deficiency and cutis laxa are genetic causes of COPD[a]	• Reduced fertility in women
• Esophagus	• Atherosclerotic peripheral vascular disease	• Childhood asthma incidence[a], poor asthma control, exacerbations of asthma in adults, asthma symptoms, wheezing severe enough to be diagnosed as asthma in susceptible children and adolescents	• Erectile dysfunction[a]
• Trachea	• Abdominal aortic aneurysm	• Chronic respiratory symptoms	• Low birth weight and fetal growth
• Acute myeloid leukemia		• Acute respiratory illness	• Ectopic pregnancy[a]
• Stomach		• Pneumonia	• Preterm delivery, still births[a], and other pregnancy complications
• Pancreas		• Mycobacterium tuberculosis disease[a] and mortality[a]	• Sudden infant death syndrome
• Kidney and ureter		• Reduced lung function	• Periodontitis
• Cervix		• Impaired lung growth	• Diabetes mellitus[a]
• Bladder		• Early onset of lung function decline	• Diminished health status[a]
• Lung and bronchus		• Lower respiratory illnesses	• Hip fractures
• Liver[a]		• Middle ear disease	• Nuclear cataracts
• Colorectal[a]		• Nasal irritation	• Macular degeneration[a]
• All-cause mortality and cancer-specific mortality in cancer patients and survivors[a]			• Low bone density in postmenopausal women
• Second primary cancers[a]			• Peptic ulcer disease in persons with Helicobacter pylori
			• Odor annoyance
			• Rheumatoid arthritis[a]
			• Inflammation and impair immune function[a]
			• Nicotine activates biological pathways through which smoking increases the risk for disease[a]

[a]Causal link reported for the first time in Surgeon General's Report in 2014

Source: The Health Consequences of Smoking—50 years of Progress: A report of the Surgeon General, 2014

Table 2.2 Causal relationships between tobacco use and exposure and respiratory diseases and conditions

Active smoking	Secondhand smoke exposure
• Lung cancer	• Lung cancer in nonsmokers
• Poor asthma control	• Stroke
• Asthma-related symptoms (i.e., wheezing) in childhood and adolescence	• Coronary heart disease morbidity and mortality
• Acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease	• Ever having asthma among children of school age
• Exacerbations of asthma in adults	• Lower respiratory illnesses in infants and children
• Chronic obstructive pulmonary disease morbidity and mortality	• Middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion
• All major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea	• Ever having asthma in school age children
• Mycobacterium tuberculosis disease and mortality	• Exposure after birth and lower level of lung function during childhood
• Premature onset of accelerated age-related decline in lung function among adults	• Cough, phlegm, wheeze, and breathlessness among children of school age
• Reduced lung function and impaired lung growth during childhood and adolescence	• Onset of wheeze illnesses in early childhood
• Early onset of decline in lung function during late adolescence and early adulthood	• Maternal smoking and persistent adverse effects on lung function across childhood
• Respiratory symptoms in children and adolescents including coughing, phlegm, wheezing, and dyspnea	
• Asthma-related symptoms (i.e., wheezing) in childhood and adolescence	
• A reduction of lung function in infants of mothers who smoked during pregnancy	
	• Odor annoyance
	• Nasal irritation

Source: The Health Consequences of Smoking—50 years of Progress: A report of the Surgeon General, 2014

tobacco exposure. The 2004 Surgeon General's report on *Smoking and Health* [7] confirmed that active smoking and involuntary exposure to tobacco smoke cause multiple preventable respiratory diseases and conditions that affect the trachea, bronchi, and lungs of the respiratory tract (see Table 2.2). Tobacco exposure increases the risk for acute respiratory illnesses, respiratory symptoms, and reduced lung function among children and adults. Data also suggest that tobacco use is

associated with asthma, idiopathic pulmonary fibrosis, bronchiolitis, influenza, Legionnaires' disease [7], and pulmonary hypertension [13]. There is growing evidence to support that respiratory bronchiolitis-interstitial lung disease [14], histiocytosis X [14], smell dysfunction [15, 16], and snoring [17] are related to tobacco exposure, but causal relationships have not yet been confirmed. The Surgeon General's report, The *Health Consequences of Smoking—50 Years of Progress*, is the first to address tuberculosis related to tobacco exposure [2]. Tobacco use and exposure are associated with about 53,795 respiratory disease-related deaths annually [8].

The mechanisms by which tobacco exposure causes and is linked to respiratory diseases and conditions are described in detail in the Surgeon General's report, *How Tobacco Smoke Causes Disease* [13]. In brief, tobacco smoke exposure moves through the mouth to the upper airways and eventually reaches the alveoli [13]. Both harmful soluble gases and particles are deposited in the airways and alveoli [13]. Tobacco use and exposure increase the exposure of the airways and lungs to toxic constituents, and over time, tobacco smoke can reduce the lung defenses to these toxins. Tobacco smoke reduces the clearance rate of particles from the lung, and 60 % of the particles from cigarette smoke are deposited in the lung [13]. Reduced particle clearance is due to the shortening, loss, or discoordination of cilia [12, 18, 19] and possibly changes in airway surface liquid including mucus visco-elasticity [12, 19, 20]. Furthermore, these particles are difficult to clear due to their high numbers, and smokers remove these particles at a slower rate [12]. The amount of particles and gases received from tobacco smoke depends on the nature of the tobacco, puff volume, air drawn in through ventilation holes of cigarettes, and local characteristics within the lung that determine the diffusion of toxic gases and the deposition of particles. The repeated exposure to these gases and particle damage to the mucociliary system increase the risk for bacterial or viral infections [13].

Tobacco-caused and tobacco-related respiratory diseases and conditions affect all smokers, but studies suggest that some racial/ethnic groups and individuals of low socioeconomic status (SES), and the intersection of these groups, suffer disproportionately from respiratory diseases and conditions. Tobacco use has also been linked to disparities in lung and other cancers and cardiovascular disease. There is adequate evidence to say that tobacco causes disparities in cancer among minority racial/ethnic groups [10, 21] and low SES groups [22]. However, it remains unclear if tobacco exposure is a cause of health disparities related to nonmalignant respiratory diseases among minority racial/ethnic groups and low SES groups in the USA.

For example, cigarette smoking is the primary cause of chronic obstructive pulmonary disease (COPD) [2]. Approximately 80–90 % of all COPD deaths are caused by smoking [23]. COPD is associated with an elevated risk of lung cancer and although African Americans have similar COPD prevalence rates as Whites [24], African American men with COPD have a sixfold increased risk for lung cancer compared to Whites [25]. African American men have the highest incidence and death rates of lung cancer in the USA [9]. Disparities in lung cancer between African American and White men and women are largely unexplained by the duration, frequency, and intensity of cigarette smoking [21, 25, 26]. In one study, 94 % of

African American men and 78 % of African American women with lung cancer also had a diagnosis of COPD [27]. These data suggest that it is possible that a respiratory diagnosis can contribute to tobacco-caused disparities in another disease category since African Americans disproportionately suffer from lung cancer incidence and mortality.

COPD can also contribute to deaths from pneumonia, ischemic heart diseases, and heart failure [20, 28–31], and heart disease disproportionately affects minority racial/ethnic groups. Deaths from heart disease, stroke, and hypertension combined are higher among African Americans compared to all other ethnic groups and almost twice that of White adults [32]. Furthermore, SHS increases adverse health outcomes among COPD patients and could adversely affect minority groups who are more likely to be exposed to SHS [33, 34]. Thus, although Whites suffer more adverse health outcomes from COPD [23], COPD increases the risk for other tobacco-caused illnesses that minority groups suffer from disproportionately.

The purpose of this chapter is to (1) provide an overview of populations in the USA who disproportionately experience disparities; (2) review current data on tobacco exposure among these groups; (3) present a framework for examining the problem; (4) discuss gaps in research and methodological challenges; and (5) provide suggestions for future research and practice.

This chapter specifically focuses on disparities in tobacco use and exposure among racial/ethnic minority and low socioeconomic groups for which there have been long-standing disparities. We report on the intersection between gender and race/ethnicity and gender and socioeconomic status (SES) when possible. There is insufficient evidence on tobacco-related health disparities in lesbian, gay, bisexual, and transgender (LGBT) individuals and populations that suffer from mental illnesses, but we report the available data. Recommendations for research and practice are made for all of these populations in the chapter summary.

Populations in the USA Who Disproportionately Experience Tobacco-Related Health Disparities

There are differences in health and indicators of health, but not all differences are health disparities and not all similarities suggest an achievement of equity. For example, smoking prevalence has declined among racial/ethnic groups, and African Americans and Whites have similar smoking rates. In 2013, current smoking was 18.3 % among African American and 19.4 % among White adults [4]. African Americans smoke fewer cigarettes per day on average, have a higher percentage of non-daily smokers, and have later age of onset of smoking compared to Whites [21, 35]. If one were to only examine these indicators, one might assume that there is equity and possibly a slight health advantage to African Americans as compared to Whites.

However, African Americans have disproportionately higher tobacco-caused cancer morbidity and mortality rates and lower survival rates. One might suggest that the lag in lung cancer rates may be due to lag in time related to smoking declines. Yet, historically, cigarettes smoking rates among African American males were not much higher than White males in 1965 and began to decline at the same time. In addition, smoking rates among African American women since 1965 have been similar to rates among White women [36], but African American women have historically had higher lung cancer incidence rates and lower 5-year survival rates than White women. These disparities are largely unexplained using the dose–response model of lung cancer. In this chapter, disparities are examined from a broad perspective, since not one indicator tells the entire story and there are multiple factors that influence the respiratory disease continuum in minority racial/ethnic and low SES groups.

Definition of Tobacco-Related Disparities

The definition of tobacco-related disparities was derived from the 2002 *National Conference on Tobacco and Health Disparities: Forging a National Research Agenda to Reduce Tobacco Related Health Disparities*, which was a meeting of national stakeholders co-sponsored by the National Cancer Institute, Centers for Disease Control and Prevention, the American Legacy Foundation, the Robert Wood Johnson Foundation, the American Cancer Society, the Campaign for Tobacco-Free Kids, the National African American Tobacco Prevention Network, and the National Latino Council on Alcohol and Tobacco. The definition was created at a time when stakeholders at local, state, and national levels were defining health disparities and seeking to increase the visibility of the need to address disparities within the USA. The consensus statement developed by this group defined tobacco-related disparities as, "differences in patterns, prevention, and treatment of tobacco use; the risk, incidence, morbidity, mortality, and burden of tobacco-related illness that exist among specific population groups in the USA; and related differences in capacity and infrastructure, access to resources, and environmental tobacco or SHS" [37].

This definition was later modified slightly by Fagan and colleagues [38] to capture more details embedded in the patterns of use that impact prevention and treatment: "tobacco-related health disparities are differences in exposure to tobacco, tobacco use initiation, current use, number of cigarettes smoked per day (cpd), quitting/treatment, relapse, and the subsequent consequences among specific groups, and include differences in capacity and infrastructure as well as access to resources".

In this expanded definition, differences in capacity, infrastructure, and access to resources are inclusive of access to care, quality of health care, socioeconomic indicators that impact health care, and psychosocial and environmental resources [38]. These definitions were intended to provide a framework for the scope of research that is needed to understand tobacco-related disparities at different points

along the tobacco-disease continuum, different trajectories that lead to health consequences, and how various social, community, and societal level factors that interact with tobacco use/exposure contribute to the development of or amelioration of tobacco-related disparities.

Populations Who Experience Tobacco-Related Disparities

In 2018, the nation will celebrate the 20-year anniversary of the publication of the 1998 Surgeon General's Report, *Tobacco Use Behaviors Among U.S. Racial/Ethnic Minority Groups* [21]. This was the first major government report to bring attention to the need to examine tobacco use and disease outcomes in minority racial/ethnic groups in the USA. This report focused on Blacks/African-Americans, Hispanic/Latino Americans (Hispanics/Latinos), American Indians and Alaska Natives (American Indian/Alaska Natives), and Asian, Native Hawaiian, and other Pacific Islander Americans. This chapter defines these groups more inclusively since data are often reported using aggregate racial/ethnic categories. This chapter also recognizes the heterogeneity within each aggregate racial/ethnic group where possible. The aggregate categories include people who come from diverse cultures, nationalities, religions, heritages, and lifestyles.

American Indians and Alaska Natives are people whose ancestors include any of the original peoples of North and South America (including Central America) and who maintain tribal affiliation or community affiliation or attachment with their indigenous group [39]. There are approximately 566 federally recognized tribes [40] and non-federally recognized tribes that have their own culture, beliefs, and practices. We use Blacks/African-Americans to be inclusive of the diverse people who self-identify as Black or African American. This category may include people of US born descent, Caribbean descent, or immigrants from other countries. Hispanic/Latino/Spanish American is an aggregate ethnic category that includes people who self-identify with at least one of these terms, and this identification is consistent with the census terminology as well. Persons who self-identify as Hispanic/Latino/Spanish American often are people from Latin American, South America, or Spain. Asian, Native Hawaiian, or other Pacific Islander Americans is an aggregate category that comprises persons of Asiatic descent and persons of Polynesian, Melanesian, or Micronesian descent. The aggregate grouping is largely based on sample size rather than similarities in origin. Furthermore, the category is somewhat misleading since these social groups convey different disease risks related to tobacco. Some studies have used Asian Americans alone or Native Hawaiian/Pacific Islander alone. Although important to report, because of the population sizes at the national levels, there are often too few data to report out specific Asian groups including Japanese, Chinese, Korean, Vietnamese, Hmong, Filipinos (many of whom will state they are of Hispanic origin), and many other Asian ethnic groups. The Native Hawaiians and Pacific Islanders category includes Native Hawaiians, Samoans, Guamanians, Chamorros, Tahitians, Tongans, Tokelauans,

Chuukese, Palauans, Yapese, Marshallese, Carolinians, Pohnpeians, Kosraeans, Nauruans, Fijians, Guineans, or Solomon Islanders, or other Pacific Islander ethnic groups [41]. Although important to report if available, Native Hawaiians and Pacific Islanders are often not reported in national data due to sample sizes, but these groups also experience disparities. In 2015, the first national survey on Native Hawaiians and Pacific Islanders was released as public data [42].

Thus, the four major minority racial/ethnic groups in the USA (American Indian/Alaska Native, Black/African American, Hispanic/Latino/Spanish American, Asian/Native Hawaiian/Pacific Islander Americans) are aggregate categories with unique ethnolinguistic characteristics; multiple ancestries; different histories of entry to the USA; diverse settlement in the USA; and different evolutions as racial, ethnic, and minority groups. None of these racial/ethnic groups represent biological groups or are necessarily used to describe one's skin color. Common factors shared by some of these racial/ethnic groups include that they have often suffered from disparities and estimates suggest that these groups will experience population growth in the next 50 years.

Overall, the USA will experience population growth and the total population will increase by 98.1 million between the years 2014 and 2060 [43] (see Table 2.3). Changes in population size are driven by births, deaths, and net international migrations [43]. The U.S. Census Bureau estimates that as the number and proportion of non-Hispanic Whites declines, the number and proportion of minority populations will increase. For example, the White population will decrease from 198 million in 2014 to 182 million in 2060, and the number and proportion of all other racial/ethnic categories will increase [43] (see Table 2.3). In 2014, minority comprised 37.8 % of the US population and in 2060 will comprise 56.4 % of the US population [43]. The actual growth of minority populations will more than double and increase from 116.2 million people in 2012 to 241.3 million by 2060 [44]. The number of

Table 2.3 Population growth estimates for racial/ethnic aggregate groups in the USA

	2014	2060
Race/ethnicity	% or number	% or number
Total population (in millions)	318,748	416,795
White alone[a]	77.7	68.5
White alone, not Hispanic or Latino	62.6	43.6
Black or African American alone[a]	13.2	14.3
American Indian and Alaska Native alone[a]	1.2	1.3
Asian alone[a]	5.4	9.3
Native Hawaiian and Other Pacific Islander[a]	0.2	0.3
Two or more races	2.5	6.2
Hispanic or Latino[b]	17.4	28.6

Source: Colby S and Ortman JM. Projections of the size and composition of the US population: 2014 to 2060, Current Population Reports, P25-1143, U.S. Census Bureau, Washington, DC 2014

[a]Includes persons reporting only one race

[b]Hispanics may be of any race, so also are included in applicable race categories

Americans of Hispanic ethnicity will more than double by 2060 and Hispanics will experience the largest increase of all racial/ethnic groups (see Table 2.3). In 2014, 48 % of children under age 18 were minority and by 2060, 64.4 % of children in the USA will be minority [43].

As minority racial/ethnic populations grow in the USA, our nation's health is not likely to improve. Minority racial/ethnic groups are over-represented at the bottom end of the socioeconomic ladder. Since 1967, median household income has both increased and decreased among racial/ethnic groups. For example, among all racial/ethnic groups, in 1967 the median household income was $43,558 and in 2013 was $51,939. Among Asians and Pacific Islanders, the median income was $63,214 in 1987 (year data were first collected) and was $70,571 in 2001 [45]. The racial/ethnic categories were then changed to separate Asians from Pacific Islanders. Among Asians, the median income was $68,143 in 2002 and $67,065 in 2013. Data are not reported for Pacific Islanders or Native Americans and Alaska Natives. Among non-Hispanic Whites, the median income was $51,380 in 1972 and $58,270 in 2013. Among Hispanics, the median income was $38,229 in 1972 (year data were first collected) and $40,963 in 2013. Among African Americans, the median income was $29,569 in 1972 and $34,598 in 2013. In 2013, the median household income among Asian Americans was more than double that in African Americans [45].

The poverty rate for all Americans was 14.7 % in 1966 and 14.5 % in 2013 [45]. For the first time since 2006, poverty rates declined from 15 % in 2012 to 14.5 % in 2013, but the number of people in poverty did not significantly change [45]. Furthermore, there have been very small fluctuations in the percent of people in poverty. In 2013, 9.6 % of Whites, 10.5 % of Asians, 10 % of Asian and Pacific Islanders, 27.2 % of African Americans, and 23 % of Hispanics lived in poverty [45]. Aggregate data, like Asian and Pacific Islander, mask some of the differences in poverty among racial/ethnic groups. For example, prior data show that American Indians, Alaska Natives, and Native Hawaiians have higher levels of poverty than Whites. If the data were aggregated with Asians, who have lower levels of poverty, then the data would be misleading. Data from the U.S. National Center for Education Statistics also show that individuals with greater educational attainment were further away from poverty than those with less education, and overall, Asians and Whites have higher educational attainment compared to the other racial/ethnic groups [46].

According to the 2014 National Healthcare Quality and Disparities Report, few disparities were eliminated. For example, advice for cessation services for African Americans decreased. Poor people generally experienced less access and worse quality health care compared to more advantaged people. Disparities in health care quality and outcomes by income and race/ethnicity are large, remained the same, and did not improve substantially through 2012 [47]. Through 2012, most disparities in access to care related to income and race/ethnicity also showed no significant change, neither getting smaller nor larger.

Improvements have been observed in health insurance coverage among adults. From 2000 to 2010, the percentage of adults aged 18–64 who were uninsured increased from 18.7 to 22.3 % [47], whereas from 2010 to 2013, the percentage

without health insurance decreased to 20.4 %. During the first half of 2014, the percentage without health insurance decreased even further to 15.6 %. Although disparities still exist in insurance coverage and African Americans and Hispanics are less likely to be insured than Whites, uninsured adults decreased from 2013 to 2014 among three racial/ethnic aggregate groups reported. In 2013, 14.5 % of Whites, 24.9 % of African Americans, 40 % of Hispanics reported being insured. In 2014, 11.1 % of Whites, 15.9 % of African Americans, and 33.2 % of Hispanics reported being uninsured. Improvement in insurance coverage is likely due to the 2010 Affordable Care Act, which as part of its implementation established marketplace enrollment in health insurance in 2013. No such declines in the uninsured population were observed among racial/ethnic groups prior the implementation of the Affordable Care Act [47]. It is important to determine whether improvements in health insurance will lead to improvements in preventive care, access to care, and quality care among the poor and minority racial/ethnic groups. As the US population becomes more diverse, it becomes more important to monitor changes in access to care and quality care among racial/ethnic and socioeconomic groups.

Tobacco Use Disparities

Racial/ethnic and SES disparities exist in tobacco use and SHS exposure. Differences in smoking prevalence rates exist by employment status, occupation, income, poverty, and education. SES, race/ethnicity, and gender often interact to increase tobacco-related disparities among these groups. We briefly review tobacco use prevalence rates among racial/ethnic and low SES groups as well as SHS exposure in these groups using the available data.

Tobacco Use Rates Among Young People

Healthy People 2020 seeks to reduce cigarette smoking among adolescents to 21 % overall and less than 16 % in the past 30 days as a strategy to help reduce tobacco-related and tobacco-caused diseases and conditions in the USA [10]. Significant progress was made in reducing cigarette smoking as a result of the 1998 Master Settlement Agreement (MSA) [48]. The MSA resulted after Attorney Generals from 46 states, five US territories, and the District of Columbia filed a lawsuit against tobacco industry to recover health care-related costs of tobacco use. Five of the largest tobacco industries paid states approximately $10 billion per year, and the MSA sets standards for the sales and marketing of cigarettes, particularly to young people. Cigarette smoking rates declined among young people after the 1998 Master Settlement Agreement from 2000 to 2009 [31] and then reached a plateau. Recent data show dramatic changes in the use of combustible versus noncombustible tobacco among middle school and high school students [49, 50].

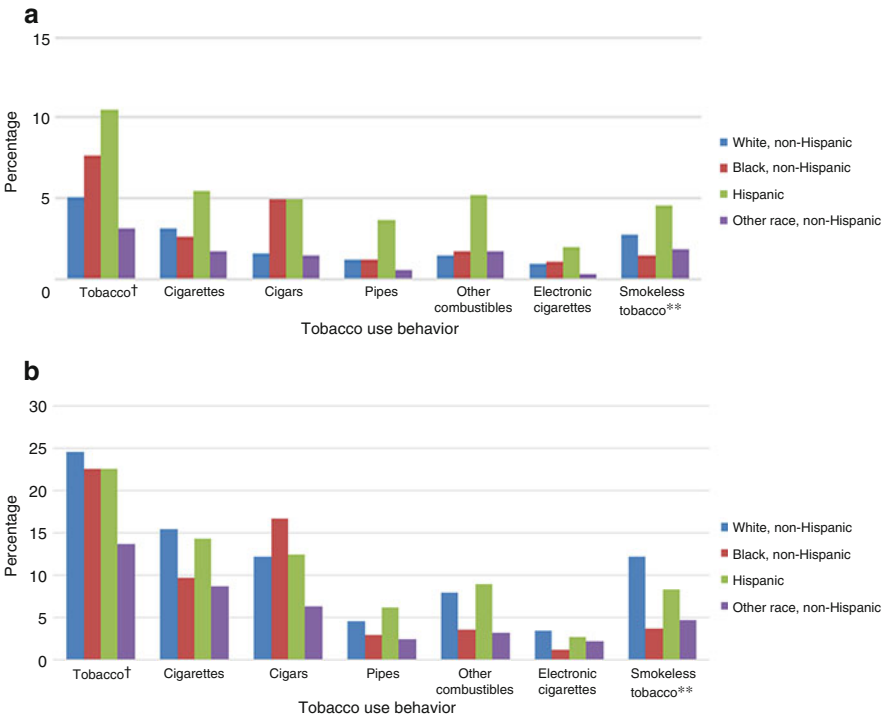

Fig. 2.1 (**a**) Percentage of middle school students currently using* tobacco products, by school level, sex, race/ethnicity, and product type—National Youth Tobacco Survey, United States, 2012. (**b**) Percentage of high school students currently using* tobacco products, by school level, sex, race/ethnicity, and product type—National Youth Tobacco Survey, United States, 2012

Among adolescents, tobacco use varies by tobacco product. Combustibles, including cigarettes and cigars, have historically been used more commonly than other tobacco products and to our knowledge, pose a higher risk for respiratory disease than noncombustibles (see Fig. 2.1). In 2012, among middle school students, past 30-day tobacco use rates were highest among Hispanics, followed by African Americans, Whites, and others, respectively. Among high school students, past 30-day tobacco use was highest among Whites, followed by African Americans, Hispanics, and others, respectively. Among middle school students, cigarette use was highest among Hispanics, but among high school students, cigarette use was most prevalent among Whites. The prevalence of cigar use was highest among African Americans, followed by Hispanic, White, and other middle and high school students, respectively [49].

In 2014, a major shift occurred in the use of combustibles and noncombustibles among young people. Past 30-day use rates of electronic cigarettes and hookah increased and surpassed past 30-day use of cigarettes overall. Among high school students, 13.4 % reported electronic cigarette use, 9.4 % reported hookah use, 9.2 %

reported cigarette use, and 8.2 % reported cigar use in the past 30 days. Among middle school students, 3.9 % reported electronic cigarette use, 2.5 % reported hookah use, 2.5 % reported cigarette use, and 1.9 % reported cigar use in the past 30 days [50].

The 2014 data also showed differences in the use of combustibles and noncombustibles by race/ethnicity. Among high school students, 10.8 % of Whites, 4.5 % of African Americans, 8.8 % of Hispanics, and 5.3 % of non-Hispanic others reported cigarette use in the past 30 days. Among middle school students, 2.2 % of Whites, 1.7 % of African Americans, and 3.7 % of Hispanics reported cigarette use in the past 30 days. Data were not reported for "other" race/ethnicity. Among high school students, 8.3 % of Whites, 8.8 % of African Americans, 8.0 % of Hispanics, and 2.6 % others used cigars in the past 30 days. Among middle school students, 1.4 % of Whites, 2.0 % of African Americans, and 2.9 % of Hispanics used cigars in the past 30 days. Data were not reported for "other" race/ethnicity [50].

Noncombustible use increased from 2012 and use rates were largely driven by increases in electronic cigarettes. Among high school students, 15.3 % of Whites, 5.6 % of African Americans, 15.3 % of Hispanics, and 9.4 % of non-Hispanic others reported electronic cigarette use in the past 30 days. Among middle school students, 3.1 % of Whites, 3.8 % of African Americans, and 6.2 % of Hispanics reported electronic cigarette use in the past 30 days. Among high school students, 9.4 % of Whites, 5.6 % of African Americans, 13.0 % of Hispanics, and 6.0 % of non-Hispanic others reported hookah use in the past 30 days. Among middle school students, 1.4 % of Whites and 5.6 % of Hispanics reported hookah in the past 30 days. Data were not reported for African American middle school students and "other" race/ethnicity [50].

The most recent data are not reported by SES indicators. Parental education has often been used as a proxy for SES [51], but the data are difficult to interpret since parental education does not necessarily predict smoking rates among adolescents.

Cigarette Use Among Adults

Healthy People 2020 seeks to reduce current cigarette smoking among adults aged 18 and over to less than 12 % as a strategy to help reduce tobacco-related and tobacco-caused diseases and conditions in the USA [10]. Smoking rates among adults are slowly declining. In 2013, an estimated 17.8 % of adults smoked cigarettes [4]. The most recent data show that smoking rates among adults are highest among individuals reporting multiple races, followed by American Indians and Alaska Natives, Whites, African Americans, Hispanics, and Asians, respectively (see Table 2.4 and Fig. 2.2). Smoking decreases with educational attainment and is higher among persons in poverty compared to persons not in poverty (see Table 2.4; Figs. 2.3 and 2.4). However, there were no significant changes from 2005 to 2013 in smoking by educational attainment status. Current smoking among persons in

Table 2.4 Percentage of persons aged >= years who were current cigarette smokers* by selected characteristics- National Health Interview Survey, United States, 2005 and 2013

	Men				Women				Total			
	2005 (n = 13,762)		2013 (n = 15,440)		2005 (n = 17,666)		2013 (n = 19,117)		2005 (N = 31,428)		2013 (N = 34,557)	
Characteristic	%	(95 % CI)	%	(95 % CI)	%	(95 % CI)	%	(95 % CI)	%	(95 % CI)	%	(95 % CI)
Overall	23.9	(22.9–24.8)	20.5	(19.5–21.4)	18.1	(17.4–18.9)	15.3	(14.6–16.1)	20.9	(20.3–21.5)	17.8	(17.2–18.4)
Race/Ethnicity[§]												
White	24.0	(22.8–25.2)	21.2	(19.9–22.4)	20.0	(19.1–20.9)	17.8	(16.8–8.8)	21.9	(21.1–22.7)	19.4	(18.6–20.2)
Black	26.7	(23.9–29.5)	21.8	(19.2–24.3)	17.3	(15.6–19.0)	15.4	(13.7–17.0)	21.5	(19.9–23.1)	18.3	(16.8–19.7)
Hispanic	21.1	(19.2–23.0)	17.3	(15.3–19.2)	11.1	(9.8–12.4)	7.0	(6.0–7.9)	16.2	(15.0–17.4)	12.1	(11.0–13.2)
American Indian/ Alaska Native	37.5	(20.7–54.3)	32.1	(20.9–43.3)	26.8	(15.5–38.1)	22.0	(12.2–31.8)	32.0	(22.3–41.7)	26.1	(18.5–33.7)
Asian[¶]	20.6	(15.7–25.5)	15.1	(12.1–18.1)	6.1	(3.7–8.5)	4.8	(3.2–6.5)	13.3	(10.4–16.3)	9.6	(7.9–11.4)
Multiple race	26.1	(16.3–35.9)	29.1	(22.0–36.2)	23.5	(14.8–32.2)	24.8	(18.0–31.5)	24.8	(17.7–31.8)	26.8	(21.9–31.8)
*Education***												
0–12 years (no diploma)	29.5	(27.2–31.8)	30.6	(27.7–33.5)	21.9	(20.0–23.7)	18.0	(16.1–20.0)	25.5	(24.0–27.1)	24.2	(22.5–25.9)
8th grade or less	21.0	(17.7–24.3)	21.9	(17.3–26.5)	13.4	(11.1–15.6)	9.2	(6.8–11.6)	17.1	(15.1–19.0)	15.4	(12.8–17.9)
9–11th grade	36.8	(33.3–40.2)	40.0	(36.0–44.0)	29.0	(26.1–31.8)	26.6	(23.2–29.9)	32.6	(30.3–34.9)	33.3	(30.6–35.8)
12th grade, no diploma	30.2	(23.5–36.9)	24.2	(18.3–30.1)	22.2	(16.9–27.5)	15.4	(11.1–19.8)	26.0	(21.8–30.2)	19.7	(16.0–23.5)
GED	47.5	(41.4–53.6)	42.9	(36.4–49.3)	38.8	(33.6–44.0)	39.7	(33.5–45.9)	43.2	(39.0–47.4)	41.4	(36.8–45.9)
High school graduate	28.8	(27.0–30.6)	26.7	(24.6–28.8)	20.7	(19.3–22.2)	17.6	(16.1–19.2)	24.6	(23.5–25.7)	22.0	(20.7–23.3)
Some college, no diploma	26.2	(24.4–28.0)	22.4	(20.4–24.8)	21.1	(19.2–22.9)	19.5	(17.8–21.3)	23.5	(22.1–24.9)	20.9	(19.4–22.3)
Associate degree	26.1	(23.3–28.9)	17.8	(15.5–20.2)	17.1	(15.0–19.3)	17.7	(15.5–20.0)	20.9	(19.2–22.6)	17.8	(16.0–19.6)

Undergraduate degree	11.9	(10.5–13.3)	10.4	(9.0–11.9)	9.6	(8.3–10.8)	7.9	(6.9–9.0)	10.7	(9.8–11.6)	9.1	(8.3–10.0)
Graduate degree	6.9	(5.3–8.5)	5.7	(4.5–7.0)	7.4	(65.9–8.8)	5.5	(4.1–6.8)	7.1	(6.0–8.3)	5.6	(4.7–6.5)
Poverty status††												
At or above poverty level	23.7	(22.6–24.8)	18.7	(17.7–19.7)	17.6	(16.8–18.5)	13.8	(13.0–14.6)	20.6	(19.9–21.3)	16.2	(15.6–16.8)
Below poverty level	34.3	(31.1–37.5)	33.8	(30.7–36.8)	26.9	(24.5–29.3)	25.8	(23.8–27.8)	29.9	(27.9–31.9)	29.2	(27.5–31.0)
Unspecified	21.2	(19.2–23.2)	10.9	(17.2–22.5)	16.1	(14.8–17.4)	12.6	(10.7–14.6)	18.4	(17.2–19.6)	16.0	(14.3–7.7)

Source: Jamal A, Agaku IT, O'Connor E, King B, Kenemer JB, Neff L. (2014). Cigarette smoking among adults—United States, 2005–2013. MMWR, 63(47); 1108–1112

§Excludes 45 (2005) and 73 (2013) respondents of unknown race. Unless indicated otherwise, all racial/ethnic groups are non-Hispanic; Hispanics can be of any race

¶Does not include Native Hawaiians or Other Pacific Islanders

**Among persons aged ≥25 years. Excludes 339 (2005) and 155 (2013) persons whose educational level was unknown

††Family income is reported by the family respondent who might or might not be the same as the sample adult respondent from whom smoking information is collected. 2005 estimates are based on reported family income and 2004 poverty thresholds published by the U.S. Census Bureau, and 2013 estimates are based on reported family income and 2012 poverty thresholds published by the U.S. Census Bureau

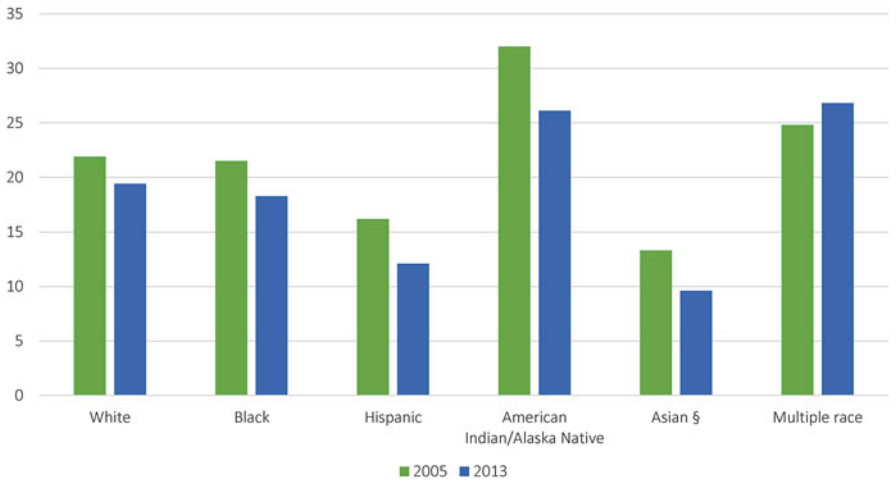

Fig. 2.2 Percentage of persons aged ≥18 years who were current cigarette smokers,* by race/ethnicity—National Health Interview Survey, United States, 2005 and 2012

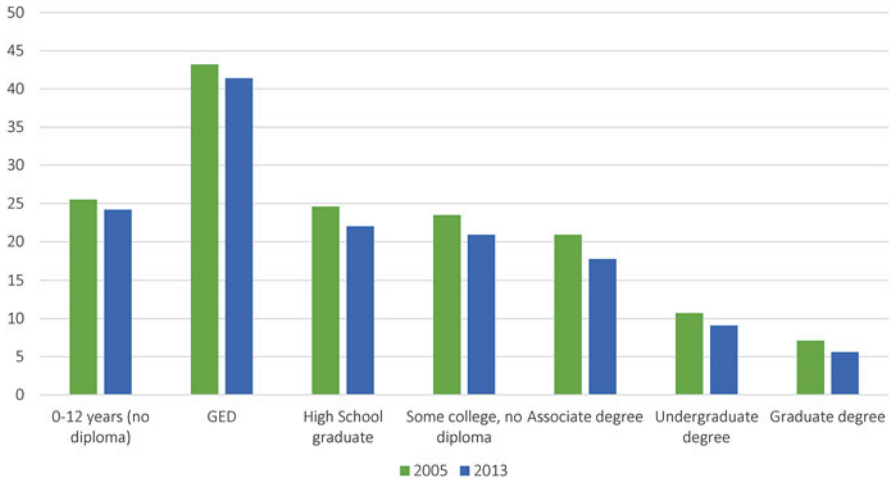

Fig. 2.3 Percentage of persons aged ≥18 years who were current cigarette smokers,* by education—National Health Interview Survey, United States, 2005 and 2012

poverty did not change in the years 2005 and 2013. Smoking rates are lower among women compared to men, but patterns of disparities by race/ethnicity and SES are similar for men and women [4].

For the first time, the Centers for Disease Control and Prevention recently reported cigarette smoking rates by sexual orientation [4]. In 2013, 26.6 % of lesbian, gay, and bisexual (LGB) persons reported current smoking compared to 17.6 % of straight adults. Among males, 26.4 % of LGB compared to 20.3 % of straight

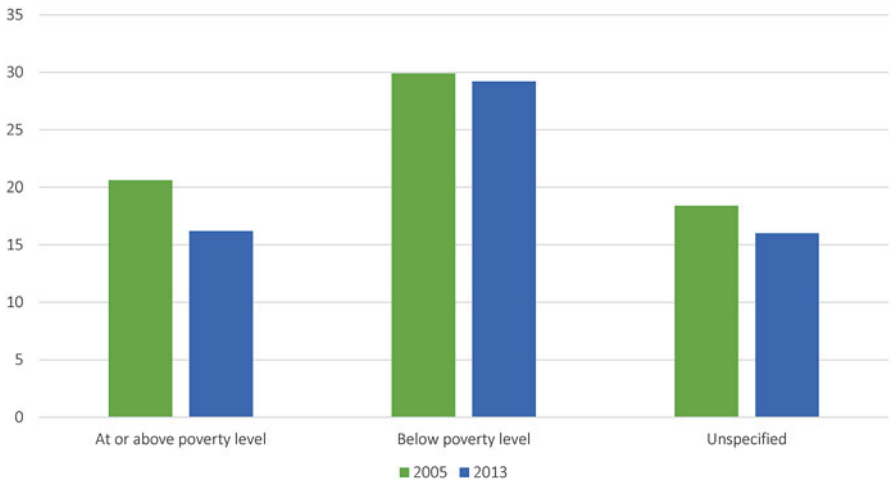

Fig. 2.4 Percentage of persons aged ≥18 years who were current cigarette smokers,* by poverty status—National Health Interview Survey, United States, 2005 and 2012

males smoked; however, these differences were not significant. Significant differences were found among females and 26.7 % of LGB smoked compared to 15 % of straight women. Data on transgender populations, a gender identity category, were not reported.

Intersection between Race/Ethnicity and SES with Mental Illness

There are limited data available on tobacco use among the mentally ill but data show that smoking prevalence rates among persons with a mental illness are almost double those of persons without a mental illness [52]. Few studies have reported on smoking among the mentally ill by race/ethnicity and SES, but smoking prevalence rates among the mentally ill reflect the specific disparities observed in the general population [52]. For example, American Indians/Alaska Natives have the highest smoking prevalence rates followed by Whites, and smoking prevalence rates among the mentally ill are highest among Native Americans and Alaska Natives followed by Whites, African Americans, Hispanics and the Asian aggregate groups. Smoking prevalence in general is highest among the least educated. Smoking rates are also highest among the least educated persons who have a mental illness and lowest among the most educated. In addition, smoking rates are also higher among the poor mentally ill compared to mentally ill smokers who are not in poverty [52] (see Table 2.5).

Table 2.5 Percentage of adults who smoke cigarettes,* by mental illness status,† sex, and selected characteristics—National Survey on Drug Use and Health, United States, 2009–2011

	% of persons with any mental illness who smoke cigarettes	% of persons with no mental illness who smoke cigarettes
	(n = 29,400)	(n = 84,700)
	%	%
Race/ethnicity§		
White	37.7	22.3
Black	34	22.3
Hispanic	31.6	19.8
American Indian/Alaska Native	54.7	30.5
Asian¶	20.6	10.4
Other	40	26.3
*Education***		
Less than high school graduate	46.6	28.9
High school graduate	40.2	25.2
Some college	38.1	21.6
College graduate	18.7	10.6
Poverty status††		
At or above poverty level	33.3	20
Below poverty level	47.9	32.8
Unknown	24.2	19.5
Total	36.1	21.4

Source: CDC (2014). Vital signs: Current smoking among adults aged. Aged ≥18 years with mental Illness—United States, 2009–2011. MMWR, February 8, 2013;62(05);81–87

§ Excludes 45 (2005) and 73 (2013) respondents of unknown race. Unless indicated otherwise, all racial/ethnic groups are non-Hispanic; Hispanics can be of any race

¶ Does not include Native Hawaiians or Other Pacific Islanders

** Among persons aged ≥25 years. Excludes 339 (2005) and 155 (2013) persons whose educational level was unknown

†† Family income is reported by the family respondent who might or might not be the same as the sample adult respondent from whom smoking information is collected. 2005 estimates are based on reported family income and 2004 poverty thresholds published by the U.S. Census Bureau, and 2013 estimates are based on reported family income and 2012 poverty thresholds published by the U.S. Census Bureau

Disparities in Secondhand Smoke Exposure

In 2006, the Surgeon General concluded there is no safe level of exposure to SHS [53]. About 49,000 tobacco-caused deaths each year are due to secondhand smoke (SHS) exposure [8]. SHS is inhaled involuntarily by nonsmokers including children, and the smoke lingers in the air hours after the cigarette has been extinguished [54].

SHS causes several nonmalignant respiratory conditions including nasal irritation, middle ear disease, respiratory symptoms, impaired lung function, lower respiratory illness, and sudden infant death syndrome. Secondhand exposure among

Table 2.6 Percentage of nonsmokers aged 3 and older with serum cotinine levels 0.05–10 ng/mL, by selected demographic characteristics—National Health and Nutrition Examination Survey, United States, 1999–2012

	% with serum cotinine 0.05–10 ng/mL (95 % CI)	
Characteristic	1999–2000	2011–2012
Total	52.5 (47.1–57.9)	25.3 (22.5–28.1)
Sex		
Male	58.5 (52.1–64.9)	27.7 (24.7–30.6)
Female	47.5 (42.5–52.5)	23.3 (20.4–26.3)
Race/ethnicity		
White, non-Hispanic	49.6 (42.4–56.7)	21.8 (18.6–24.9)
Black, non-Hispanic	74.2 (70.2–78.2)	46.8 (30.8–55.6)
Mexican–American	44.3 (37.4–51.1)	23.9 (16.3–31.4)
Poverty status		
Below poverty level	71.6 (64.8–78.5)	43.2 (37.3–49.0)
At or above poverty level	48.8 (42.8–54.8)	21.2 (18.8–23.6)
Unspecified	53.5 (48.4–58.6)	31.7 (22.8–40.5)
Education aged 25 and older		
≤Grade 11	53.9 (48.7–59.0)	27.6 (23.0–32.2)
High school diploma or equivalent	51.6 (44.5–58.6)	27.5 (21.2–33.7)
Some college or associate degree	48.2 (40.8–55.6)	21.2 (17.5–24.9)
≥College diploma	35.2 (27.5–43.0)	11.8 (9.1–14.4)
Own or rent home		
Own	45.8 (39.3–52.3)	19.0 (16.1–22.0)
Rent	68.1 (61.6–74.6)	36.8 (32.3–41.3)

Source: Homa DM, Neff LJ, King BA, Caraballo RS, Bunnell RE, Babb SD, Garrett BE, Sosnoff CS, Wang L. (2015). Vital Signs: Disparities in Nonsmokers' Exposure to Secondhand Smoke—United States, 1999–2012. MMWR, February 6, 64(04);103–108

children is associated with acute respiratory infections, middle ear disease, exacerbated asthma, respiratory symptoms, and decreased lung function [7]. Prior reports have confirmed that some minority racial/ethnic and low socioeconomic groups are disproportionately exposed to SHS. If smoking rates are higher among some minority racial/ethnic groups, then one might hypothesize that secondhand smoke would be higher as well. However, disparities in SHS exposure exist, but do not mirror cigarette smoking rates as noted in Tables 2.4 and 2.6. For example, SHS exposure among African Americans is more than double that of Whites. Moreover, Mexican Americans have higher SHS exposure than Whites, yet cigarette smoking is higher among Whites than Hispanics. These disparities in SHS exposure likely influence children's risk of tobacco-caused respiratory conditions and diseases.

The principal indicator used to determine tobacco smoke exposure in nonsmokers is cotinine, which is the primary metabolite of nicotine [55]. Nicotine is first metabolized to cotinine and cotinine is metabolized to *trans* 3′ hydroxycotinine, a process which is almost exclusively mediated by the enzyme cytochrome P450 2A6 (CYP2A6) [56]. Data show that SHS exposure as measured by detectable serum cotinine levels 0.05 to

10 ng/mL has significantly declined overall from 1999/2000 to 2011/2012 [57]. Despite these declines, according to the most recent data, a considerably higher proportion of non-Hispanic African American nonsmokers were exposed to SHS than other groups, and current exposure is double that of non-Hispanic Whites (see Table 2.6).

African Americans have similar smoking rates as Whites, so observed differences in SHS exposure among nonsmokers may be due to differences in policy implementation, but could also be related to differences in nicotine metabolism. African American smokers have lower odds of having smoke-free policies in the home compared to non-Hispanic Whites [58]. However, even among children who are not exposed to SHS in the home, non-Hispanic Blacks have significantly higher serum cotinine levels compared to non-Hispanic Whites [59].

Research indicates that nicotine metabolism varies by gender [44] and race/ethnicity [60, 61], and some studies show that menthol also influences the metabolism of nicotine in the liver [62]. Study findings suggest that African Americans have slower rates of nicotine metabolism as indicated by cotinine and the nicotine metabolite ratio, which is highly correlated with rates of nicotine clearance [63] and the CYP2A6 genotype, which is primarily responsible for nicotine metabolism [64, 65]. African American nonsmokers exposed to tobacco smoke may have slower nicotine metabolism like African American smokers.

Nationwide, about 76–88 % of African Americans smokers consume menthol-flavored cigarettes [66–68] compared with 26 % of the Asian/Pacific Islander smokers [49], 28 % of Hispanic smokers, and 22 % of White smokers [66, 67]. Data from Hawaii also show that 78 % of Native Hawaiian/Pacific Islander aggregate category of smokers use menthols [69]. Menthol inhibits the metabolism of nicotine in liver microsomal test systems [70, 71] by slowing oxidative metabolism and glucuronide conjugation [71]. Some studies have demonstrated higher cotinine levels [71, 72] among menthol smokers compared to non-menthol smokers [72, 73]. However, other studies have not shown higher cotinine levels among menthol compared to non-menthol smokers [74, 75] Because race/ethnicity, gender, menthol, and other factors may influence nicotine metabolism, additional studies are needed to determine how these factors are related to and influence the assessment of SHS exposure and health disparities.

Data show declines in SHS exposure, but still indicate significant differences in SHS exposure by poverty status (see Table 2.6). In 2011–2012, a significantly greater percentage of nonsmokers living in poverty had serum cotinine levels 0.05–10 ng/mL compared to their more economically advantaged counterparts (43.2 % vs. 21.2 %) [57]. In another study, SHS exposure in the home was significantly higher among children and adolescents from families with annual income less than $20,000 (26.4 %) compared to those earning $20,000 or more (15.5 %) [59]. To our knowledge, studies have not examined poverty as an environmental factor that influences the metabolism of nicotine to cotinine, but it is likely that the data reflect true differences in SHS exposure among nonsmokers.

While SHS exposure has declined overall, there continues to be differences by educational attainment (see Table 2.6). Among nonsmokers with less than 11 years of education, 27.6 % were exposed to SHS, 27.5 % with a high school education or equivalent, 21.2 % with a college or associates degree, and 11.8 % with a college

degree or more [57]. These data also show significantly higher serum cotinine levels among children from families with lower annual family incomes and lower householder educational levels even in homes where they did not have exposure to SHS in the home [57]. It is possible that children of disadvantage may not only be disproportionately exposed to SHS inside the home, but perhaps outside the home and in other social environments. Data on SHS exposure is also reported at the national level by home ownership, which is another indicator for SES. SHS exposure declined among both homeowners and renters yet remained significantly higher among renters (see Table 2.6).

It is clear that SHS exposure is associated with respiratory disease, but whether or not disparities in SHS exposure lead to disparities in respiratory diseases and conditions like middle ear disease, respiratory symptoms, impaired lung function, sudden infant death syndrome, and nasal irritation is not clear. There are genetic variations in CYP2A6, and studies suggest this enzyme can bioactivate tobacco-specific pre-carcinogens including (methyl-nitrosamino)-1-(3pyridyl)-1-butanone (NNK) [75] and *N*′-nitrosonornicotine (NNN) which have been associated with lung cancer [76] in addition to its role in nicotine metabolism. However, it is not clear if CYP2A6 is related to nonmalignant respiratory diseases.

Tobacco Causes Respiratory Health Disparities and Populations Impacted by Disparities

Americans are living longer, and life expectancy has increased for most populations in the USA. In 2012, the life expectancy for all Americans was 79 years according to the World Bank [77]. The USA was only ranked 26th out of 36 countries that are members of the Organisation of Economic Cooperation and Development with respect to life expectancy [78]. Factors such as health care system fragmentation, large uninsured population, socioeconomic conditions, and enormous income inequalities may contribute to relatively modest life expectancy gains in the USA compared to other countries [78]. Notably, respiratory disease is a large contributor to lower life expectancy among Americans, and tobacco use exposure is a major cause of respiratory diseases and conditions in the USA. Other chapters in this book will specifically address health disparities in COPD, asthma, lung cancer, and tuberculosis, which are all related to tobacco exposure with respect to risk and/or exacerbation of disease.

Framework for Examining the Problem

To better understand tobacco-related health disparities among different groups, it is important to have a framework for examining the issue (Fig. 2.5). Asthma is used as an example since it is a chronic respiratory condition associated with smoking as well as individual, social, and environmental factors; access to care and treatment issues; and health policy.

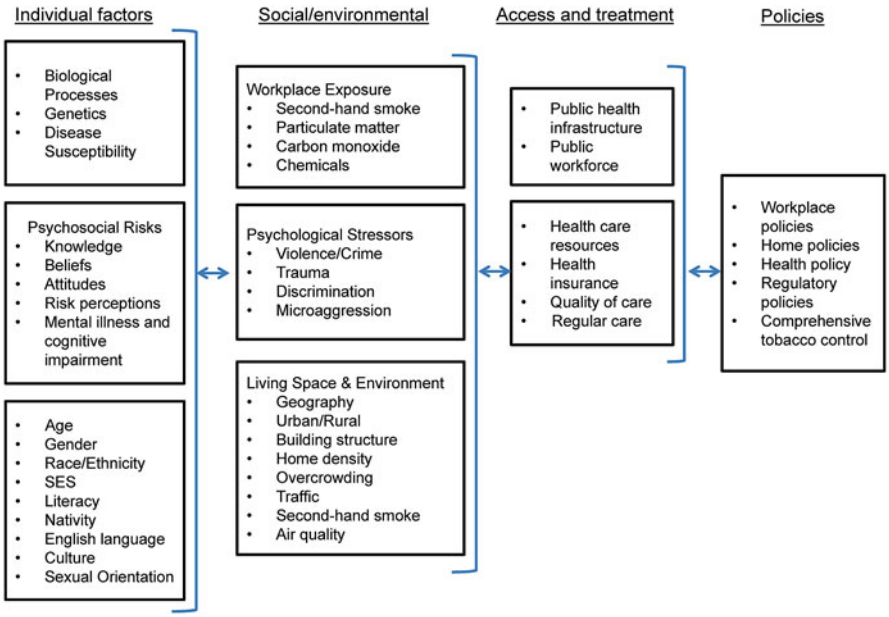

Fig. 2.5 Framework for examining disparities in tobacco-related respiratory diseases and conditions

Figure 2.5 suggests that there are individual level factors that put smokers and persons exposed to smoke at risk for respiratory diseases and conditions. While research is not well developed in this area, there may be biological processes and differences in disease susceptibility that either increase or decrease the risk for respiratory symptoms among smoking or SHS-exposed asthmatics. Knowledge, attitudes, beliefs, and risk perceptions related to tobacco use may influence personal decisions about smoking or parental decisions to smoke around children, which increases their risk for asthma and exacerbates asthma symptoms. Sociodemographic factors, literacy, nativity, culture, and use of English language may influence help-seeking behaviors related to the treatment of asthma.

Social and environmental factors may influence air quality independent of tobacco smoke exposure, which may further exacerbate asthma. Moreover, social and environmental factors may affect where asthma care is received (e.g., patients may go to emergency rooms to receive care instead of receiving ongoing regular care). Furthermore, policies such as smoke-free multi-unit housing may improve air quality and reduce asthma incidence among children. Persons who rent will benefit since they are disproportionately exposed to SHS exposure. Social and environmental factors and related policies are important to understanding health disparities because minorities are more likely to live in poor environments. For example, African American and Hispanic individuals are more likely than Whites to live in environmental spaces with high levels of air toxins [79]. Minorities are also more

likely to live in communities near freeways and areas with high traffic, which increases their exposure to air toxins [80–82]. To date, the mechanisms by which interactions between environmental exposures and tobacco use affect respiratory disease risk remain poorly understood.

Policies to Reduce Tobacco-Related Respiratory Diseases

Tobacco policies have been implemented primarily to reduce smoking and SHS exposure. For example, clean-indoor air laws and policies in workplaces, restaurants, bars, and other public places; voluntary smoke-free home policies; federal and state tobacco taxes; age of purchase laws; restrictions on advertising and promotion; and youth access restrictions are important components of a comprehensive tobacco control program to reduce tobacco use initiation, increase smoking cessation, and reduce SHS. The Family Smoking Prevention and Tobacco Control Act of 2009 (Public Law 111–31, U.S. Statutes at Large 123) [83] has allowed government, for the first time, to have the authority to regulate a legal but lethal product. Moreover, the Patient Protection and Affordable Care Act (Public Law 111–148, U.S. Statutes at Large 124) [84] passed in 2010 requires insurance companies, including Medicaid, to cover tobacco cessation treatments as a strategy to reduce barriers to access to cessation treatments.

From a societal perspective, it is important to understand not only the impact of tobacco control on trends [85] in smoking and SHS exposure among racial/ethnic and SES minority groups, but also the effects on disease rates as well. For example, the 2014 Surgeon General's report concluded that there was sufficient evidence to infer that smoke-free laws and policies reduce coronary events in persons younger than 65 years of age. Further investigation is needed to determine if policies can eliminate cardiovascular disease disparities. Lung cancer rates are declining among most racial/ethnic groups [9], but African American males still show the highest incidence and death rates from lung cancer. Further investigation regarding the impact of tobacco policies on respiratory diseases such as lung cancer and COPD is warranted. Understanding how tobacco control programs affect respiratory disease beyond their impact on smoking rates alone will help influence policymaker decisions and governmental strategies to decrease smoking-related health disparities and decrease the overall burden of tobacco.

Limitations and Methodological Challenges

This chapter focuses on disparities in tobacco smoking and smoke exposure among different groups in the USA, examining differences by gender, race/ethnicity, age, and socioeconomic status. However, the evidence available to examine these disparities is limited by several factors. For example, death rates due to smoking-related respiratory

diseases are often reported in aggregate form, and thus it may be difficult to distinguish differences in specific conditions by race/ethnicity or SES. On the other hand, death rates reported in disaggregate form by race/ethnicity may be difficult to generate due to the small sample sizes of many racial/ethnic groups. In general, there is limited information available regarding the relationship between tobacco exposure and respiratory disease and conditions among minority racial/ethnic groups, but there is even less data for Native Americans, Alaska Natives, Native Hawaiians, and Pacific Islanders. While these groups account for less than 2 % of the US population, the limited evidence suggests that disparities exist, and population numbers should not drive the generation of scientific evidence that would facilitate the health of populations, though they may be small in number. In most cases, data for these groups are either not reported or collapsed into a single "other" category. Response rates are also low for national surveys. The National Health Interview Survey, which is used to report adult current smoking annually, had a 61.2 % response rate in 2013 [4]. Nonresponse can introduce bias and result in under-reporting of smoking rates, particularly among racial/ethnic minority and low SES groups.

We have reported on interactions between gender–race/ethnicity and gender–SES where possible, but these data are often not available for all groups due to small sample sizes. We do not focus on pregnant women as a disparate population in this chapter but believe it is critical to our nation's health to examine the relationship between tobacco exposure and respiratory illnesses among pregnant women and their children. This review also has limited information on health disparities in LGBT populations since there is little data available at this time. New national data were reported on LGB smoking, but not transgender smoking, for the year 2013. LGB data were not reported by race/ethnicity or SES [4]. Further investigation is warranted on tobacco use and exposure by race/ethnicity, SES, LGBT status, and their associations with tobacco-related disease. Finally, prevalence data on smoking among the mentally ill have recently been reported at the national level, but tobacco-related respiratory diseases and conditions for these groups are not reported at the national level. Thus, our understanding of the impact of smoking among individuals with mental illness relative to the US population at large remains limited.

This report does not focus on smokeless tobacco, cigars of any kind, kreteks, hookahs/waterpipes, pipes, electronic cigarettes/vaporizers, or any other form of tobacco/nicotine, although we report some data for youth. The investigation of how new and emerging products like flavored electronic cigarettes, cigars of any kind, and hookah/waterpipes contribute to respiratory diseases and conditions is critical since the landscape of tobacco use is changing, particularly among young people who may benefit the most from early cessation of these products.

Directions for Future Research

Approximately 42.1 million Americans smoked in 2013 [4], and we are not likely to reach our Healthy People 2020 goals to reduce cigarette smoking to 12 % among adults. As a result, progress in reducing health disparities for tobacco-related diseases will also likely be delayed. The landscape of tobacco control is changing and has expanded to include more combustibles and also many popular flavored non-combustibles. Such changes may reverse progress made to reduce tobacco use among youth and potentially establish new pathways for disparities.

Moving forward, the power of the Food and Drug Administration Center for Tobacco Products to have a significant impact on tobacco control will depend on their ability to overcome legal and lobbying challenges by the tobacco industry, to circumnavigate the boundaries of operating within the federal government system, and to garner public support for regulatory policies that may benefit public health. The Affordable Care Act may be a game changer for those with the least health care access who are also often those at greatest risk for smoking and tobacco-caused respiratory diseases.

In future research, it is important that we monitor dual and poly-tobacco use and its impact on respiratory diseases and conditions. Young people are more likely than older people to use multiple forms of tobacco along with alcohol, marijuana, and other drugs. About 30 % of young adult cigarette smokers report dual use of tobacco products [86]. Young adults who currently use cigarettes are also at increased risk for electronic cigarette use [87] and are more likely to use flavored little cigars and cigarillos [88–90]. To date, there is limited data regarding the effects of poly-tobacco use on respiratory disease risk and progression. Furthermore, we have limited data on dual and poly use of substances among racial/ethnic minority and low SES groups.

Because national surveys cannot capture sufficient data to report respiratory diseases for Native Hawaiians and Pacific Islanders, Filipinos, Native Americans, Alaska Natives, Asian ethnic, and Hispanic ethnic groups, it is important to collect state and local data that would allow for the accurate reporting of tobacco-related respiratory diseases in these minority groups. These populations are growing, and by 2060, there may be sufficient numbers of different Hispanic ethnic groups to report data at the national level. However, this is unlikely to be the case for other minority groups in the USA. Data can be collected at the national level for LGBT populations and for the mentally ill since there are sufficient numbers of these groups. It is recommended that data on the prevalence and death rates of tobacco-related respiratory diseases should be reported by these factors and by race/ethnicity, poverty status, and gender when possible.

Longitudinal data on tobacco-related respiratory diseases are evolving, but it has been challenging to track how the prevalence and death rates of tobacco-related respiratory diseases are related to tobacco exposure trajectory data among minority racial/ethnic and low SES groups in the USA. In addition to studying prevalence and death rates over time, it is important to examine other health indicators such as hospitalization and quality of life in individuals with tobacco-related diseases.

Furthermore, knowledge, attitudes, and beliefs and health care access and quality may influence disease outcomes related to tobacco exposure among different groups, and therefore warrant further study.

Future research should also examine the differential disease causal pathways of tobacco exposure and increase our understanding of who is at greatest risk for each tobacco-related disease. Tobacco-caused diseases may be consequences of multiple pathways, multiple mechanisms toward those pathways, and the interactions of genes and environmental factors that modulate the activities of the pathways [13]. Understanding these mechanisms can help us better target disease prevention strategies including the implementation of policies that target specific products and product constituents, like nicotine, menthol, and other flavors. A better understanding may also allow us to develop new approaches, such as using biomarkers in early stage disease diagnosis or genetic counseling for smoking cessation programs that specifically seek to eliminate disparities [13].

Further study is needed to understand how socioeconomic status may influence the risk of tobacco-related respiratory diseases and their outcomes and how this intersects with health disparities in racial/ethnic minorities. Cumulative adverse health effects result from living in poverty [91, 92], and poor individuals are more likely to die prematurely than higher income persons [91, 92].

Summary and Conclusions

In summary, minority racial/ethnic group populations are growing in the USA. It is not expected that the nation will grow healthier with as the population of those who experience health and socioeconomic disparities increases. Understanding how tobacco exposure impacts diseases among these groups is important to the planning of targeted public health initiatives to curtail disease growth with population growth. Forward thinking and planning will also help to reduce health care costs associated with disparities as minority populations in the USA increase in numbers.

Smoking has declined among all racial/ethnic and socioeconomic groups. However, some minority racial/ethnic and low SES groups continue to suffer disproportionately from tobacco use and exposure. These use patterns, however, do not convey disease risk. Lower use of tobacco is not directly associated with lower risk of tobacco-caused chronic conditions. Nor is higher tobacco use associated with higher risk of tobacco-caused illnesses. Tobacco control continues to be a top public health priority, as we know that quitting smoking, reducing the initiation of tobacco use, and eliminating SHS exposure will ultimately reduce tobacco-caused diseases and deaths and improve the quality of life for many Americans. Different strategies may be needed for different groups since declines in smoking despite existing interventions are not equivalent for all groups.

References

1. Centers for Disease Control and Prevention (CDC). Achievements in public health, 1900–1999: tobacco Use—United States, 1900–1999. MMWR. 1999;48(43):986–93. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4843a2.htm.
2. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the surgeon general. Atlanta: U.S. Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2014.
3. Agaku IT, King BA, Dube SR, Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults—United States, 2005–2012. MMWR Morb Mortal Wkly Rep. 2014;63(2):29–34.
4. Jamal A, Agaku IT, O'Connor E, King BA, Kenemer JB, Neff L. Current cigarette smoking among adults—United States, 2005–2013. MMWR Morb Mortal Wkly Rep. 2014;63(47):1108–12.
5. Centers for Disease Control and Prevention (CDC). Vital signs: nonsmokers' exposure to secondhand smoke—United States, 1999–2012. MMWR Morb Mortal Wkly Rep. 2015;64(04):103–8.
6. World Health Organization report on the global tobacco epidemic. 2011. http://www.who.int/tobacco/global_report/2011/en/.
7. US Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2004.
8. Centers for Disease Control and Prevention (CDC). Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000–2004. MMWR Morb Mortal Wkly Rep. 2008;57(45):1226–8.
9. Surveillance epidemiology and end results program. http://seer.cancer.gov/faststats/. Accessed 25 Apr 2015.
10. Healthy people 2020. https://www.healthypeople.gov/2020/topics-objectives/topic/tobacco-use/objectives#5287. Accessed 23 July 2015.
11. US Department of Health, Education, and Welfare. Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control; 1964. PHS Publication No 1103.
12. US Department of Health and Human Services. The health consequences of smoking: chronic obstructive lung disease. A report of the Surgeon General. Rockville: US Department of Health and Human Services/Public Health Service/Office on Smoking and Health; 1984.
13. US Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease. A report of the US Surgeon General. Atlanta: US Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2010.
14. Caminati A, Harari S. Smoking-related interstitial pneumonias and pulmonary Langerhans cell histiocytosis. Proc Am Thorac Soc. 2006;3(4):299–306.
15. Vent J, Robinson A, Gentry-Nielsen M, Conley D, Hallworth R, Leopold D, et al. Pathology of the olfactory epithelium: smoking and ethanol exposure. Laryngoscope. 2004;114:1383–8.
16. Murphy C, Schubert C, Cruickshanks K, Klein B, Klein R, Nondahl D. Prevalence of olfactory impairment in older adults. JAMA. 2002;288(18):2307–12.
17. Franklin K, Gíslason T, Omenaas E, Jõgi R, Jensen E, Lindberg E, et al. The influence of active and passive smoking on habitual snoring. Am J Respir Crit Care Med. 2004;170:799–803.

18. Leopold P, O'Mahony M, Lian X, Tilley A, Harvey B, Crystal R. Smoking is associated with shortened airway cilia. PLoS One. 2009;4(12):e8157.
19. Stanley PJ, Wilson R, Greenstone MA, MacWilliam L, Cole PJ. Effect of cigarette smoking on nasal mucociliary clearance and ciliary beat frequency. Thorax. 1986;41(7):519–23.
20. Vilkman S, Keistinen T, Tuuponen T, Kivelä SL. Survival and cause of death among elderly chronic obstructive pulmonary disease patients after first admission to hospital. Respiration. 1997;64:281–4.
21. US Department of Health and Human Services. Tobacco use among U.S. racial/ethnic minority groups. A report of the US Surgeon General. Atlanta: US Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 1998.
22. Singh GK, Miller BA, Hankey BF, Edwards BK. Area socioeconomic variations in U.S. Cancer Incidence, Mortality, Stage, Treatment, and Survival, 1975–1999. NCI Cancer Surveillance Monograph Series, Number 4. Bethesda: National Cancer Institute; 2003. NIH Publication No. 03-5417.
23. American Lung Association (ALA). Trends in COPD morbidity and mortality. http://www.lung.org/finding-cures/our-research/trend-reports/copd-trend-report.pdf. Accessed 24 July 2014.
24. Centers for Disease Control and Prevention (CDC). Chronic obstructive pulmonary disease among adults—United States, 2011. MMWR Morb Mortal Wkly Rep. 2012;61(46):938–43.
25. Etzel CJ, Kachroo S, Liu M, D'Amelio A, Dong Q, Cote ML, Wenzlaff AS, Hong WK, Greisinger AJ, Schwartz AG, Spitz MR. Development and validation of a lung cancer risk prediction model for African–Americans. Cancer Prev Res (Phila). 2008;1(4):255–65. doi:10.1158/1940-6207.CAPR-08-0082.
26. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, Le Marchand L. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med. 2006;354(4):333–42.
27. Mina N, Soubani AO, Cote ML, Suwan T, Wenzlaff AS, Jhajhria S, Samarah H, Schwartz AG. The relationship between chronic obstructive pulmonary disease and lung cancer in African American patients. Clin Lung Cancer. 2012;13(2):149–56.
28. Takiguchi Y, Sekine I, Iwasawa S, Kurimoto R, Tatsumi K. Chronic obstructive pulmonary disease as a risk factor for lung cancer. World J Clin Oncol. 2014;5(4):660–6. doi:10.5306/wjco.v5.i4.660. Review.
29. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233–9.
30. Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med. 1999;340:1948–53.
31. Zieliński J. Circumstances of death in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis. 1998;53:324–30.
32. Centers for Disease Control and Prevention (CDC). Vital signs: avoidable deaths from heart disease, stroke, and hypertensive disease—United States, 2001–2010. MMWR Morb Mortal Wkly Rep. 2013;62(35):721–7.
33. Eisner MD, Balmes J, Yelin EH, Katz PP, Hammond SK, Benowitz N, Blanc PD. Directly measured secondhand smoke exposure and COPD health outcomes. BMC Pulm Med. 2006;6:12.
34. Eisner MD, Jacob 3rd P, Benowitz NL, Balmes J, Blanc PD. Longer term exposure to secondhand smoke and health outcomes in COPD: impact of urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Nicotine Tob Res. 2009;11(8):945–53.
35. US Department of Health and Human Services. Prevention tobacco use among youth and adults: A report of the US Surgeon General. Atlanta: US Department of Health and Human

Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2012.
36. CDC. Cigarette smoking—United States, 1965–2008. MMWR. 2011;60(Suppl):109–13.
37. Fagan P, King G, Lawrence D, Petrucci SA, Robinson RG, Banks D, Marable S, Grana R. Eliminating tobacco-related health disparities: directions for future research. Am J Public Health. 2004;94(2):211–7.
38. Fagan P, Moolchan ET, Lawrence D, Fernander A, Ponder PK. Identifying health disparities across the tobacco continuum. Addiction. 2007;102 Suppl 2:5–29.
39. Census brief 2010 and American Indian tribes. http://www.census.gov/prod/cen2010/briefs/c2010br-10.pdf. Accessed 24 July 2014.
40. U.S. Department of Interior Indian Affairs. http://www.bia.gov/WhoWeAre/BIA/OIS/TribalGovernmentServices/TribalDirectory/. Accessed 23 Apr 2015.
41. Census and Asian and Pacific Islanders. www.census.gov/prod/cen2010/briefs/c2010br-12.pdf. Accessed 24 July 2014.
42. http://www.cdc.gov/nchs/nhis/nhpi.html. Accessed 23 Apr 2015.
43. Colby S, Ortman JM. Projections of the size and composition of the U.S. population: 2014 to 2060, Current Population Reports, P25-1143, U.S. Census Bureau, Washington, DC 2014.
44. U.S. Census growth 2060. https://www.census.gov/newsroom/releases/archives/population/cb12-243.html. Accessed 24 July 2014
45. Income and poverty in the United States: 2013 U.S. https://www.census.gov/prod/2014pubs/p60-248.pdf. Accessed 23 Apr 2015.
46. National Center for Educational Statistics. http://nces.ed.gov/programs/coe/indicator_caa.asp. Accessed 24 July 14.
47. 2014 National Healthcare Quality & Disparities Report. 2015. Rockville: Agency for Healthcare Research and Quality. http://www.ahrq.gov/research/findings/nhqrdr/nhqdr14/index.html.
48. Master settlement agreement. http://publichealthlawcenter.org/sites/default/files/resources/master-settlement-agreement.pdf. Accessed 26 Apr 2015.
49. Centers for Disease Control and Prevention (CDC). Tobacco product use among middle and high school students—United States, 2011 and 2012. MMWR Morb Mortal Wkly Rep. 2013;62(45):893–7; Erratum in: MMWR Morb Mortal Wkly Rep. 2013 Nov 22;62(46):940.
50. Arrazola RA, Singh T, Corey CG, Husten CG, Neff LJ, Apelberg BJ, Bunnell RE, Choiniere CJ, King BA, Cox S, McAfee T, Caraballo RS. Tobacco use among middle and high school students—United States, 2011–2014. MMWR Morb Mortal Wkly Rep. 2015;64(14):381–5.
51. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. American teens more cautious about using synthetic drugs. Ann Arbor: University of Michigan News Service; 2013. http://www.monitoringthefuture.org. Accessed 18 Dec 2013.
52. Centers for Disease Control and Prevention (CDC). Vital signs: current cigarette smoking among adults aged ≥18 years with mental illness—United States, 2009–2011. MMWR Morb Mortal Wkly Rep. 2013;62(5):81–7.
53. US Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services/Centers for Disease Control and Prevention/Coordinating Center for Health Promotion/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2006.
54. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, prepared by the Office of Environmental Health Hazard Assessment (OEHHA). http://www.oehha.org/air/environmental_tobacco/pdf/app3partb2005.pdf. Accessed 24 July 2014.
55. Benowitz NL, Jacob III P. Metabolism of nicotine to cotinine studied by a dual stable isotope method. Clin Pharmacol Ther. 1994;56:483–93.
56. Messina ES, Tyndale RF, Sellers EM. A major role for CYP2A6 in nicotine C-oxidation by human liver microsomes. J Pharmacol Exp Ther. 1997;282(3):1608–14.

57. Homa DM, Neff LJ, King BA, Caraballo RS, Bunnell RE, Babb SD, Garrett BE, Sosnoff CS, Wang L. Vital signs: disparities in Nonsmokers' exposure to secondhand smoke—United States, 1999–2012. MMWR Morb Mortal Wkly Rep. 2015;64(04):103–8.
58. Fernander A, Rayens MK, Hahn E, Zhang M, Adkins SM. Menthol smoking, smoke-free policies and cessation services. Addiction. 2010;105 Suppl 1:105–14. doi:10.1111/j.1360-0443.2010.03189.x.
59. Marano C, Schober SE, Brody DJ, Zhang C. Secondhand tobacco smoke exposure among children and adolescents: United States, 2003-2006. Pediatrics. 2009;124(5):1299–305. doi:10.1542/peds.2009-0880. Epub 2009 Oct 19.
60. Kandel DB, Hu MC, Schaffran C, Udry JR, Benowitz NL. Urine nicotine metabolites and smoking behavior in a multiracial/multiethnic national sample of young adults. Am J Epidemiol. 2007;165(8):901–10.
61. Caraballo RS, Giovino GA, Pechacek TF, Mowery PD, Richter PA, Strauss WJ, Sharp DJ, Eriksen MP, Pirkle JL, Maurer KR. Racial and ethnic differences in serum cotinine levels of cigarette smokers: Third National Health and Nutrition Examination Survey, 1988–1991. JAMA. 1998;280(2):135–9.
62. MacDougall JM, Fandrick K, Zhang X, Serafin SV, Cashman JR. Inhibition of human liver microsomal (S)-nicotine oxidation by (−)-menthol and analogues. Chem Res Toxicol. 2003;16(8):988–93.
63. Dempsey D, Tutka P, Jacob 3rd P, Allen F, Schoedel K, Tyndale RF, Benowitz NL. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther. 2004;76:64–72.
64. Malaiyandi V, Goodz SD, Sellers EM, Tyndale RF. CYP2A6 genotype, phenotype, and the use of nicotine metabolites as biomarkers during ad libitum smoking. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1812–9.
65. Johnstone E, Benowitz N, Cargill A, Jacob R, Hinks L, Day I, et al. Determinants of the rate of nicotine metabolism and effects on smoking behavior. Clin Pharmacol Ther. 2006; 80(4):319–30.
66. Lawrence D, Rose A, Fagan P, Moolchan ET, Gibson JT, Backinger CL. National patterns and correlates of mentholated cigarette use in the United States. Addiction. 2010;105 Suppl 1:13–31.
67. Rock VJ, Davis SP, Thorne SL, Asman KJ, Caraballo RS. Menthol cigarette use among racial and ethnic groups in the United States, 2004–2008. Nicotine Tob Res. 2010;12 Suppl 2: S117–24.
68. Giovino GA, Villanti AC, Mowery PD, Sevilimedu V, Niaura RS, Vallone DM, Abrams DB. Differential trends in cigarette smoking in the USA: is menthol slowing progress? Tob Control. 2015;24(1):28–37. doi:10.1136/tobaccocontrol-2013-051159.
69. Smoking and Tobacco in Hawaii. Figures and trends (July 2010). http://hawaii.gov/health/healthy-lifestyles/tobacco/resources/general/trends.pdf. Accessed 26 Mar 2012.
70. Benowitz NL, Herrera B, Jacob 3rd P. Mentholated cigarette smoking inhibits nicotine metabolism. J Pharmacol Exp Ther. 2004;310(3):1208–15.
71. Clark PI, Gautam S, Gerson LW. Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers. Chest. 1996;110(5):1194–8.
72. Caskey NH, Jarvik ME, McCarthy WJ, Rosenblatt MR, Gross TM, Carpenter CL. Rapid smoking of menthol and nonmenthol cigarettes by black and white smokers. Pharmacol Biochem Behav. 1993;46(2):259–63.
73. Ahijevych K, Parsley LA. Smoke constituent exposure and stage of change in black and white women cigarette smokers. Addict Behav. 1999;24(1):115–20.
74. Jones MR, Apelberg BJ, Tellez-Plaza M, Samet JM, Navas-Acien A. Menthol cigarettes, race/ethnicity, and biomarkers of tobacco use in U.S. adults: the 1999–2010 National Health and Nutrition Examination Survey (NHANES). Cancer Epidemiol Biomarkers Prev. 2013;22(2):224–32. doi:10.1158/1055-9965.EPI-12-0912.

75. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer. 2003;3(10):733–44; Review. Erratum in: Nat Rev Cancer. 2004;4(1):84.
76. Yamazaki H, Inui Y, Yun CH, Guengerich FP, Shimada T. Cytochrome P450 2E1 and 2A6 enzymes as major catalysts for metabolic activation of N-nitrosodialkylamines and tobacco-related nitrosamines in human liver microsomes. Carcinogenesis. 1992;13(10):1789–94.
77. World Bank. http://data.worldbank.org/country/united-states.
78. Health at a glance, 2013, OECD indicators, OECD Publishing. http://gallery.mailchimp.com/de3259be81e52e95191ab7806/files/HAG2013.pdf.
79. Morello-Frosch R, Lopez R. The riskscape and the color line: examining the role of segregation in environmental health disparities. Environ Res. 2006;102(2):181–96.
80. Gunier RB, Hertz A, Von Behren J, Reynolds P. Traffic density in California: socioeconomic and ethnic differences among potentially exposed children. J Expo Anal Environ Epidemiol. 2003;13(3):240–6.
81. Chakraborty J, Zandbergen PA. Children at risk: measuring racial/ethnic disparities in potential exposure to air pollution at school and home. J Epidemiol Community Health. 2007;61(12):1074–9.
82. Green RS, Smorodinsky S, Kim JJ, McLaughlin R, Ostro B. Proximity of California public schools to busy roads. Environ Health Perspect. 2004;112(1):61–6.
83. Family smoking prevention and tobacco control act. http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf.
84. The affordable care act. http://www.hhs.gov/healthcare/rights/law/.
85. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, Levy DT. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964–2012. JAMA. 2014;311(2):164–71. doi:10.1001/jama.2013.285112.
86. Villanti AC, Richardson A, Vallone DM, Rath JM. Flavored tobacco product use among U.S. young adults. Am J Prev Med. 2013;44(4):388–91.
87. Pokhrel P, Little MA, Fagan P, Muranaka N, Herzog TA. Electronic cigarette use outcome expectancies among college students. Addict Behav. 2014;39(6):1062–5.
88. Borawski EA, Brooks A, Colabianchi N, et al. Adult use of cigars, little cigars, and cigarillos in Cuyahoga County, Ohio: a cross-sectional study. Nicotine Tob Res. 2010;12(6):669–73.
89. Cullen J, Mowery P, Delnevo C, Allen JA, Sokol N, Byron MJ, Thornton-Bullock A. Seven-year patterns in US cigar use epidemiology among young adults aged 18–25 years: a focus on race/ethnicity and brand. Am J Public Health. 2011;101(10):1955–62.
90. King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among U.S. middle and high school students. J Adolesc Health. 2014;54(1):40–6.
91. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff (Millwood). 2002;21(2):60–76.
92. Marmot M. The influence of income on health: views of an epidemiologist. Health Aff (Millwood). 2002;21(2):31–46.

Chapter 3
Health Disparities Related to Environmental Air Quality

Sonali Bose and Gregory B. Diette

Key Points

- Air pollution, including both indoor and outdoor sources, has significant negative impact on respiratory morbidity and mortality.
- Health disparities related to environmental air quality and its associated outcomes have been identified with respect to socioeconomic status, race, gender, age, and geographic location.
- Mechanisms that may be responsible for health disparities related to environmental air exposure include differential exposure, differential susceptibility, and differences in social coping.

Introduction

It has been more than 50 years since the Great London Smog drew the world's attention to the poisonous health effects of air pollution. For an entire greater city area, industrial fumes permeated down to the street level, suffocating clouds replacing all breathable air. Sulfurous smoke, trapped in both outdoor spaces and within buildings, shrouded the visual world of every Londoner (Fig. 3.1). Unable to escape such a pervasive exposure, Londoners succumbed to an additional 12,000 deaths, as well as numerous ER visits and hospital admissions, during and in the immediate months after this environmental tragedy [1].

Since that time, air pollution has been recognized as a major health concern across the globe, and unfortunately, this has not been purely limited to discrete events in time and space. There has been growing appreciation that chronic or

S. Bose, M.D., M.P.H. • G.B. Diette, M.D., M.H.S., (✉)
Division of Pulmonary and Critical Care Medicine,
Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: gdiette@jhmi.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_3

Fig. 3.1 An image of London during the Great Smog of 1952. The tall buildings in the background are completely masked by the thickly polluted air. Source: Getty Images

repeated exposures to elevated airborne levels of particles and gases are responsible for short- and long-term adverse health outcomes in populations living in both industrialized and developing areas [2, 3]. In most cases, poor air quality has not been an undiscriminating uniform plague across people as it was in London in 1952. Rather, patterns of exposure to air pollution have evolved into a complex mosaic of disparities across lines of race, gender, age, geography, and socioeconomic strata. Concentrations of gaseous and particulate matter in the airborne microenvironment of defined subpopulations may vary at both local and regional levels, resulting in meaningful differences in health among these groups.

In this chapter, we will explore the unequal effects of air pollution across subpopulations divided by these lines. We will begin by reviewing the key air pollutants that are known to result in adverse respiratory health and their sources, then describe these health effects, and finally survey the evidence supporting disparities among subgroups. While not a comprehensive review, our discussion will reveal the complexities behind the ways in which different populations in the world suffer the varied consequences of airborne environmental hazards.

Air Pollutants

Ambient air pollution is often a toxic mixture of gaseous and particulate components, of which six primary air pollutants—sulfur dioxide (SO_2), particulate matter (PM), ozone, nitric oxide (NO_2), carbon monoxide (CO), and lead—have been

Table 3.1 Major air pollutants and common sources

Pollutant	Source
$PM_{2.5}$, $PM_{2.5–10}$	Natural sources: windblown soil, pollen, spores, sea salt, volcanic ash
	Man-made sources: road/street dust, agricultural and construction activities, particles from industrial and vehicular combustion, tobacco smoke, cooking activities
NO_x, NO_2	High-temperature combustion activities from stationary sources such as thermal powerplants and incinerators, cooking, and mobile sources such as automobiles
O_3	Produced in the atmosphere from photochemical reactions induced by ultraviolet light between pollutant nitrogen oxides (NO_x) and volatile organic compounds. Levels typically vary throughout the day and across seasons depending on intensity of sunlight and temperature
SO_2	Combustion by-product of fuels such as coal and petroleum. Sources include industrial emissions from refineries, diesel fumes, paper factories. Natural sources include volcanic eruptions
CO	Burning of fossil or other organic fuels, vehicular exhaust, forest fires, volcanic eruptions
Lead	Industrial sources such as exhaust from vehicles using leaded gasoline, smelters

$PM_{2.5}$: Particulate matter (PM) of less than 2.5 μm in diameter; $PM_{2.5–10}$: PM of sizes between 2.5 and 10 μm in diameter. Adapted from Arbex et al. [3]

individually demonstrated to bear health impact (Table 3.1). Certain pollutants were labeled as criteria pollutants after the 1970 Clean Air Act in the USA set standards to specifically limit each of their outdoor emissions. Another significant source of pollution worldwide is environmental tobacco smoke (ETS), which is now perhaps the most well known of the air pollutants because of its widely-recognized adverse health effects. The impact of ETS is discussed elsewhere in this book and will not be specifically dealt with in this chapter.

Among the six criteria pollutants, sulfur dioxide (SO_2) is one that most commonly originates from the burning of fossil fuels such as coal and petroleum in power plants and factories, as well as in the burning of fuels for various vehicles and locomotive equipment [4]. In the case of the Great London smog, the severe cold led Londoners to burn more coal that winter, which along with the city's usual industrial emissions, resulted in levels of SO_2 and particles of several thousands of μg per m^3. Although the institution of the Clean Air Act in the USA has resulted in an overall decline in SO_2 emissions since 1970, elevated airborne concentrations continue to persist in regional portions of North America today and are subject to oxidation into sulfuric acid as the gas disperses across high altitudes and mixes with other particles and liquids [4].

The interaction of sulfur gases with the environment generates a mixture that notably also includes particles. In hindsight, these particles may have been the component of the London black smoke responsible for most of the ensuing health effects [4]. Particulate matter (PM) itself is a complex mixture of solids and/or liquid particles of various sizes and is classified by its aerodynamic equivalent diameter (PM_{10} (<10 μm), $PM_{2.5}$ (<2.5 μm), and $PM_{0.1}$ (<0.1 μm)), which is important in that

particle size affects the ability to penetrate and deposit in human airways. Fine particles such as those <2.5 μm and ultrafine particles <0.1 μm have the greatest propensity to deposit further down into the air spaces, in contrast to larger particles which are trapped by the mucociliary apparatus of the nose and the upper airway. Whether from natural sources such as soil/dust, fires, and volcanoes, or from man-made sources such as industry, smoking, and usual human activity, PM has been shown to play a significant role in overall and cardiopulmonary mortality and morbidity with both short- and long-term exposures [5].

Another primary pollutant is ozone, a highly reactive gas that is synthesized from photochemical reactions when UV light reacts with other pollutants such as nitrous oxides and volatile organic compounds in the atmosphere. The majority of exposure to ozone is in the ambient outdoor environment, with indoor ozone only generated by specific appliances or by penetration of outdoor air into indoor spaces. High levels in the ambient air are noted especially in the summer months in the USA and with acute exposures, can induce noticeable respiratory symptoms (chest pain, cough) as well as underlying airway inflammation and cellular injury [4].

In contrast to ozone, NO_2 has gained recent interest as both an ambient and an indoor air pollutant. Indoor NO_2 is generated by the burning of fossil fuels and is released from the operation of gas and kerosene stoves, heaters, and furnaces, often not vented to the outdoors. The effects of airborne NO_2 may have particular implications for those with underlying respiratory conditions such as asthma and COPD [6, 7]. The last two criteria pollutants, carbon monoxide and lead, are both by-products of industrial and vehicular combustion and tend to be concentrated in urban areas, though levels of lead have diminished since the reduction in the use of vehicular leaded gasoline [4]. Lead has been associated with adverse health effects not wholly limited to the respiratory system, often with particular relevance to fetal, infant, and child neurocognitive development [8].

Impact on Respiratory Health

The evidence that has accumulated over the last half century linking acute and chronic exposures of these major air pollutants to morbidity and mortality is significant, and ongoing studies continue to strengthen such associations [9]. Particulate matter, for example, has been estimated to contribute to 800,000 premature deaths in the world annually [5]. Early studies of mortality from long-term outdoor exposures such as the “Harvard Six Cities” study and related follow-up studies observed that inhabitants of the most polluted cities had increased rates of all-cause and cardiopulmonary mortality compared to less polluted cities [5]. Subsequent studies that focused specifically on respiratory outcomes demonstrated associations between incremental increases in ambient PM and increased respiratory symptoms, lower lung function, and increased healthcare encounters for pulmonary disorders such as asthma and COPD, as well as more frequent lung infections in children and adults. The mechanisms behind such relationships have been proposed to involve

the ability of particulates to induce inflammatory responses in human airway epithelial cells, which in turn cause oxidative stress and further airway damage [5].

Similarly, pollutants such as ozone are cytotoxic to cells in the airway and are also associated with local inflammatory responses and injury that may underlie the observed decrements in lung function and increase in bronchial hyper-reactivity. Some studies support the relationship of high-ozone days with increased hospital admissions for respiratory illness such as asthma [4], though it is difficult to separate the effects of ozone from the combined effects of other commonly occurring co-pollutants, thereby warranting further single-pollutant studies.

Ongoing efforts to fully characterize the health effects of air pollution have yielded consistent findings that link airborne exposures to respiratory morbidity but in ways not previously well understood. A recent multi-cohort study in Europe found ambient air pollution, particularly PM, to be linked to lung cancer [10], and new evidence on the relationship of increases in indoor NO_2 to more severe asthma and COPD symptoms has led to work aimed at developing interventions to reduce indoor exposures [6, 7, 11]. This and future work will help to elucidate the true breadth of air pollution's impact on human health.

Sources of Pollutants

As described above, air pollution can originate from both natural and anthropogenic sources, and patterns of dispersion have greatly been affected by global climate change and the spread of industrialization over the last century. Regardless of the source, human exposure to air pollution is unfortunately ubiquitous, and the type and extent of these exposures depend not only on where they are being generated but also on lifestyle factors that shape where individuals spend their time. Meteorological factors also play a major role, since ambient temperatures and weather conditions motivate varying degrees of insulation and ventilation in constructed spaces, which in turn affects the communication of outdoor and indoor environments.

In the USA, Americans spend over 90 % of their time inside [12], and therefore indoor sources of pollution can have a significant impact on health. Moreover, despite the impact of the Clean Air Act on ambient pollution, indoor levels of air pollution are not centrally monitored or regulated and therefore may pose unrecognized hazards for those who spend extended periods of time indoors. Indoor environments where people spend most of their time are commonly divided into three realms: the household, the school, and the workplace.

The level of exposure in each of these places relies on such characteristics as the type and frequency of activities being performed, the degree of enclosure and ventilation patterns of the building, and any efforts to filter or shield from the inhalation of airborne gases and particles. For example, common household activities have been known to generate high indoor levels of particulate matter. In one study of urban homes in Baltimore, three major sources of particulate matter in the homes

were identified: smoking, sweeping, and stove use, with increasing frequency of these behaviors significantly associated with increasing levels of PM_{10} measured in the indoor air [13]. Cleaning activities contribute to indoor pollution, not only from the emissions from toxic cleaning agents used themselves, but also due to the re-suspension of particles in the settled dust. Similarly, NO_2 concentrations within the home are correlated to both the presence of a gas stove and gas heater, as well as use of a space heater or stove/oven for heat [6], demonstrating the effects of cooking activities upon the generation of indoor NO_2. Besides cleaning and cooking, other activities such as the burning of candles or incense, use of fireplaces/wood stoves and certain appliances, and smoking are common indoor sources of air pollution in the developed world.

In contrast, the burden of household air pollution in the developing regions of the world is largely the result of indoor burning of biomass fuels. Almost half of the world, mostly in the poorest of settings, depends on the burning of cheaper, but energy-inefficient, organic materials such as animal dung, charcoal, and crop waste, as well as kerosene and mixed fuels, in open fires in order to cook and heat homes. The indoor levels of smoke and particulate matter generated from this burning are orders of magnitude above those seen in developed regions and have been linked to significant mortality and morbidity from acute respiratory infections/pneumonia, COPD, and airway cancers [14].

Many of the same indoor activities common to personal residences pertain to school environments. Cleaning and heating activities within school buildings may contribute more to indoor levels of pollution. One specific source of indoor pollution relevant to schools that has gained recent interest is school bus exhaust-related pollutant exposure. Due to the common phenomenon of bus "idling" while waiting to pick up and drop off children at schools, as well as the general transport of children within buses, exposure to diesel fumes inside and around buses has been found to be a measurable source of particulate matter, elemental carbon, carbon monoxide, and other gaseous and particulate pollutants [15, 16]. This exposure has led to considerable concern regarding the effects of noxious diesel fumes on young children, and further research on this is underway.

A third portion of indoor time for a large number of the world's adult population is spent at work. Occupational hazards remain a concern as the cause for a variety of acute and chronic respiratory conditions, including exposures that span from airborne industrial toxins to aerosolized agricultural pollutants to the common indoor exposures from routine human activity discussed above. Given its large scope, work-related exposures and their health impact is specifically discussed in another chapter of this book.

In contrast to the variety of indoor pollutant exposures thus far described, outdoor pollution often affects large populations at once and is not readily amenable to lifestyle modifications by the exposed individual. Pollution sources can be described as "stationary" sources, such as factories with smoke stacks, and "mobile" sources such as motor vehicle tail pipes [4]. Despite the lessons learned during the 1952 London Great Smog and other similar environmental disasters, industrial emissions continue to be a major source of ambient pollution, particularly in urban areas.

Combustion of fuels by power plants, factories, and waste incinerators that directly release organic, acidic, and metallic compounds into the air, continue to dominate as sources of ambient pollution. Historically, in an effort to improve local air quality, industrial smoke stacks have been redesigned to be taller, removing their emissions from the mixing layers nearer to the ground and from the breathable air of the people who live around them [4]. However, the emissions from these tall stacks, which are often at higher temperature and linger longer in the suspended air, become more widely dispersed and are capable of blanketing a larger geographical area [17]. In contrast, domestic chimneys and other low-lying emissions disperse less and accordingly, contribute greater to local airborne pollution [17]. Vehicular traffic is another example of low-lying emissions that can rapidly elevate concentrations of particulate and gaseous pollution in the direct breathing space of an individual. Not only do vehicles contribute through by-products of combustion released from tail pipes, but operation of these vehicles over often long pathways of transport generate particulate emissions into the air that are released from tire wear and road abrasion [17].

Lastly, natural sources of outdoor pollution such as soil, dust, volcanic eruptions, and organic material such as pollen and fungi, can contribute significantly to ambient levels of particulate matter and gases and can cause meaningful health effects. For example, volcanic activity is known to release a unique diversity of particles and volatiles such as SO_2, CO, CO_2, HCL, HF, H_2S, and radon in ash [18]. In the case of the Eyjafjallajökull eruption in Iceland, up to 25 % of the ash was found to be less than 10 μm, well within the respirable range. Health effects of such eruptions can extend for great distances, as in the case of Icelandic events that led to fallouts across the European continent, and can manifest with acute respiratory effects including symptoms of airway irritation and exacerbations in people with asthma and chronic bronchitis [18].

Evidence for Disparities

Disparities in the exposure to, and health effects from, air pollution are a uniquely relevant dilemma due to the intimate association between the environment and respiratory system. Thus, the inequalities in the environment that characteristically divide groups often coexist with differences in air quality, which in turn lead to disparities in respiratory health. Experts describe three mechanisms that may translate variations in the air quality of microenvironments into further differences in the health of their inhabitants [19]. The first is "differential exposure" where certain groups are found to be more exposed to air pollution sources, thereby violating the principle of environmental justice, which upholds that no one population should bear the brunt of toxic exposure over another [20]. The second mechanism is that of "differential susceptibility," such that a given exposure to air pollution may have different effects on an individual due to specific personal and social vulnerabilities of people in a group. This is especially relevant to those individuals with pre-existing

Table 3.2 Pathways of environmental health disparities

Mechanism	Example
Differential exposure	A family who lives upon a major congested road. The exposure to traffic-related air pollution is higher for these individuals than those who may live on a private street
Differential susceptibility	A young child in this household who plays in the front yard. He/she, as an active child, has higher minute ventilation and may have a less-developed immune system compared to the adults in the home, rendering him/her more susceptible to respiratory illness
Social coping	The family has an income below the poverty line, and as a result cannot afford to relocate to avoid the pollution exposure, to enroll their child to a safer play environment, or to obtain private insurance to cover healthcare when the child becomes ill, all options which would minimize their risk of pollution-related health effects

lung disease such as asthma and COPD. Lastly, the "social coping" mechanism includes factors that relate to socioeconomic status that may modify the ability of an individual to manage risk imposed by the threats faced, such as adequate access to healthcare [21]. These mechanisms are useful to consider when assessing the true burden of poor air quality for specific groups (Table 3.2).

In the following sections, we will discuss the evidence for disparities in air pollution across various dividing lines—socioeconomic status, race, gender and age, and geography. While many of these divisions overlap, they highlight the ways in which various groups of people around the world disproportionately bear the burden of global air pollution.

Socioeconomic Status

Over the last several decades, inequalities in health across socioeconomic strata have been recognized for a variety of health outcomes. In one study comparing 22 nations across the European continent, those countries with lower socioeconomic status (SES) (as measured by education, occupation, and income) had higher mortality and poorer health assessments [22]. Inequalities in overall mortality across Europe were found to be attributable to differences in rates of cardiovascular, smoking-, and alcohol-related mortality between people of different educational backgrounds. Moreover, variations between countries with regard to the relative contribution of these disease-specific mortalities were also found. In respiratory disease, inequalities between the rich and the poor have been recognized, with asthma morbidity known to be higher in areas in the USA with greater poverty [23]. While the exact causes of this phenomenon are incompletely understood, the link between poverty and lung disease illustrates the interdependence of socioeconomically driven environmental factors and respiratory health and reinforces the notion that pollution may have differential effects upon people who are disadvantaged.

To further understand this relationship, we can consider the conclusions of the WHO Commission on Social Determinants of Health, which attributed physical environments, among other factors pertaining to an individual's living circumstances, to observed disparities in health [24]. As poverty itself may predispose disadvantaged groups to spend more time in poor-quality housing, work in toxic environments, and engage in hazardous behaviors (e.g., smoking) that directly affect surrounding air quality, greater exposure to a physically-damaging environment in disadvantaged circumstances would allow for further downstream inequalities of health [25].

As the Great London smog event illustrated, among the most pervasive of poor quality environments is that of polluted air. Subsequent work from other European studies has supported that chronic levels of air pollution are associated with disadvantaged populations, potentially more so than other environmental threats. Evidence for social inequalities being linked to higher concentrations of PM, NO_2, and SO_2 can be found across European nations, though there are a few studies demonstrating conflicting data with regard to the strength and direction of these relationships [19]. Despite such variations in findings regarding differential exposure highlighted by one set of reviewers, the authors conclude that as a whole, individuals from disadvantaged socioeconomic brackets suffer greater effects from air pollution and speculate that this is mediated perhaps by additional mechanisms such as comorbid conditions or social coping which may impact individual vulnerability [19].

In the United States as well, several studies support that persons of lower socioeconomic status are preferentially exposed to greater air pollution. An analysis of counties across the USA revealed that those areas with the worst air quality, as measured by annual and daily $PM_{2.5}$, were also the poorest, compared with those counties with the best air quality [26]. In another report from North Carolina, predicted estimates of $PM_{2.5}$ concentrations were 0.10 μg/m^3 lower with each increase in interquartile range of median household income [27], further demonstrating that the burden of air pollution may disproportionately fall upon socioeconomically disadvantaged communities. More specific work by Bell and colleagues found that estimated exposure to the specific components of $PM_{2.5}$ was higher for those who had less than a high school education and for unemployed persons, with larger disparities between the groups in some of the individual particle components than in $PM_{2.5}$ overall [28]. Such exposures may have long-term health consequences, with several studies demonstrating that there is an increased risk of mortality related to $PM_{2.5}$ exposure among groups of lower education and income [25, 29].

Perhaps the largest socioeconomic inequality which greatly impacts exposure to air pollution is one which affects three billion people worldwide, primarily in developing regions. Biomass fuel combustion is one of the worst polluters of the indoor environment and preferentially affects the world's poor due to the fact that biomass fuels are among the cheapest of fuels. Its low rung on the "energy ladder," whereby fuels low in cost also are least efficient and produce more pollution [14], results in

a higher burden of pollution-related adverse respiratory effects among individuals living in parts of the world that cannot afford cleaner fuels. Since women and children are the most affected by domestic activities that require solid fuel, biomass burning will be discussed in greater detail in a later section of this chapter.

Race

The disparities across socioeconomic strata discussed above are often difficult to parse out from overlapping inequalities related to race. However, in North America, there is a rich racial diversity that allows for recognition of specific race-related differences in exposure to air pollutants, and the evidence thus far is most telling regarding inequalities between Caucasian and African-American populations. Using information from the US EPA Air Toxics Data which estimates the airborne concentration of 148 chemicals in more than 60,000 US census tracts, a survey of a series of 44 metropolitan areas in the US found that in each and every geographical area, blacks were more likely to live in highly polluted areas than their white counterparts, with varying degrees of disparity in each metropolis [30]. Another study specifically assessed exposures to $PM_{2.5}$ and found that non-Hispanic blacks had higher exposures than other racial subgroups [26]. As a follow-up to these results, a third study specifically examined 14 components within $PM_{2.5}$ and found that African-Americans experienced the highest estimated exposures for 13 out of the 14 components compared to Caucasians [28].

Black–white segregation patterns have been suggested as an influential force in the design of this unequal distribution of exposures [30, 31]. The effects of segregation on air pollution exposure may encompass broader themes of implicit racial discrimination that limit black individuals' options to pursue housing and occupational choices away from highly polluted areas [30]. The role of segregation in mediating disparities in environmental exposures between African-Americans and other racial minorities is a topic of active research.

Inequalities in exposures between racial groups may partially explain the ongoing conundrum as to why blacks in the USA experience a disproportionate burden of respiratory health morbidity compared to whites, such as higher rates of asthma-related ER visits, hospitalizations, and deaths [32]. Data from the 2002 to 2005 National Health Interview Survey suggested that associations between higher ambient $PM_{2.5}$ exposure and asthma morbidity were strongest among non-Hispanic blacks compared to whites, illustrating an effect modification upon the relationship between air pollution and health outcomes by race [33]. Some effect of race itself in respiratory disease susceptibility seems to be independent of differences in environmental exposure, socioeconomic status, and other factors; among over 9000 children studied across four US cities, black children continued to be more likely to report asthma compared to white children in the same cities even after consideration of these factors [34]. Further studies are needed to identify factors yet unaccounted for that mediate these disproportionate effects between racial subgroups.

Gender

A recent review of the relationship between gender and air pollution explored the evidence that women and men may experience distinct differences in environmental exposures and effects [35]. To begin with, the author of this review reminds us that appropriate assessment of this disparity requires the distinction of gender, which is a personally-assigned identity that implies social roles and activities, from sex, which is biologically assigned and may implicate differences that stem from chromosomal or hormonal characteristics. Both classifications are relevant to the disparities in the burden of air pollution worldwide. Gender and sex differences may both be additionally modified by developmental life stage, and thus adults and children have generally been studied within their own cohorts. Studies that report stronger effects in boys are balanced by other studies demonstrating that pollution may affect girls more, with inequalities attributed to age, gender variations in types and location of play activities, differences in lung structure/function and growth rates, and hormonal differences [35]. Additionally, unlike the dichotomous nature of sex assignment, differential exposure between gender groups can vary greatly across societies, depending on ethnic, cultural, and religious behaviors that shape how and where people spend their time. Finally, similar to differences in health effects across SES and race, differences in the effects of air pollution between genders and sexes are complex and may be the result of multiple amplifying stages, starting with inequalities in ambient pollution exposure, followed by differences in the effective exposure dose, and lastly with regard to differential susceptibility related to the biologic response of the lung to inhaled toxins [16].

Among adults, differential exposures to air pollution between men and women are often driven by occupational stratification, which affects risk of job-related hazards. In many societies where men are likely to be in the public workforce, occupational exposures related to ambient pollution from industry or agriculture may dominate, whereas women who are domestically involved, either in their own homes or the homes of others, may have exposures related to indoor household activities (cooking, cleaning, etc.).

Nowhere is this gender disparity more striking than in the exposure of women in developing nations to indoor air pollution from biomass burning. Household air pollution from the use of biomass fuels has been studied across the Indian subcontinent, Africa, and Latin America [36]. Approximately three billion people worldwide rely on the use of inefficient types of solid fuel as their major source of energy, and burning animal dung, wood, and crop residues for cooking and heating often takes place in open fires within the home. In these circumstances, women, and the children they often carry on their backs while working around the stove, are the primary victims [37]. The amount of time women spend in direct contact with active burning can be anywhere from 3 to 7 h each day, but gases and particles that are generated continue to fill the indoor atmosphere beyond the burn time [38]. The indoor air pollution generated from these burning activities is composed of over 200 airborne chemicals of which over 90 % are respirable, including pollutants such as PM (both PM_{10} and $PM_{2.5}$), SO_2, $N0_2$, and poly-aromatic hydrocarbons.

The level of PM_{10}, for example, can average between 300 and 3000 μg/m^3 in a day, with peak levels as high as 10,000 μg/m^3 [38]. This is in stark comparison to US Environmental Protection Agency *annual* exposure limit of 50 μg/m^3. Particulate matter has thus far proven to be the most detrimental of the pollutants in biomass burning to human health.

Increasing evidence has highlighted the ill health effects suffered from such chronic exposure to these toxic levels of indoor pollution throughout a woman's lifetime. Of these, the most important is the development of chronic obstructive pulmonary disease (COPD). In the developed world, COPD is known more commonly to be a smoker's disease, but globally, the majority of COPD is in nonsmokers globally, with biomass exposure as the most likely culprit. In India, for example, an estimate of 20,000–155,000 deaths annually occur due to COPD in women and are attributable to household air pollution [36]. Dose response studies have revealed that hours and years of accumulated exposure to biomass smoke increases the likelihood of decreased pulmonary function and risk of chronic bronchitis [39]. One meta-analysis estimated that the odds ratio for developing COPD with exposure compared to no exposure was 2.40, a risk comparable to smoking [40]. Several of the components of biomass smoke are known carcinogens, and as a result, in addition to obstructive lung diseases, upper airway and lung adenocarcinomas have been associated with biomass smoke exposure as well [38]. Lastly, the effects of the exposure on children will be discussed in more detail below. Overall, the World Health Organization has estimated that approximately two million premature deaths each year can be attributed to indoor biomass-generated air pollution, rendering indoor air pollution a serious health issue, specifically for the women of the world.

A large focus of sex-related disparities of air pollution has centered around the effects on reproductive health and pregnancy. Prenatal effects of air pollution exposure, such as that of indoor biomass smoke, include low birth weight [41, 42]. Other sources of ambient pollution including traffic-related air pollution in the USA and Europe have also been found to be negatively associated with fetal growth [43–46]. Low birth weight in turn may have long-term consequences in the eventual achievement of lung function and risks for asthma [45] in these offspring, implying that the adverse effects of air pollution in women can have indelible effects lasting beyond a generation.

Age

The phenomenon of indoor biomass smoke exposure not only highlights women as a subgroup that has disproportionate exposure to air pollution, but it also draws attention to the welfare of children as well. In developing countries, young children are frequently exposed to solid fuel pollution within the home while they are being cared for by their mothers. For many of these children, this exposure may have started in utero which may confer a particular disadvantage with regard to their lung development and susceptibility to additional airborne insults postpartum. In fact,

infants born to women with biomass exposure during pregnancy have lower birth weight [41, 42]. Furthermore, the exposures to indoor air pollution have been found to translate into an excess of acute respiratory infections (2–3 times increased risk, compared to unexposed children), which are the most common cause for childhood deaths in the world. In fact, more than half of all deaths attributed to biomass smoke exposure occur among children under 5 years of age [38].

In the industrialized nations of the world such as the USA and Europe, indoor air pollution also plays a significant role in respiratory morbidity. In the USA, children spend most of their time indoors. In addition to being in school and in mass transport vehicles which have their own specific environmental exposures described earlier, children spend an average of 6 h a day indoors at home engaging in activities such as watching television and playing video games [47]. Furthermore, older children may begin to become engaged in the workforce, which has potential for occupational exposures. Unfortunately, in these ways, the lifestyle of children often facilitates exposure to the pollution generated by other members of the household and workplace.

The effects of air pollution from other indoor and outdoor sources on children are also well described in the literature, especially among children with pre-existing lung disease such as asthma. In a recent review of existing panel studies, increasing concentrations of particulate matter have been shown to be associated with increased respiratory symptoms and decreased lung function [48]. A systematic review of the short-term effects of PM revealed predominantly adverse effects on respiratory symptoms and lung function [49]. Similar work supports the effects of NO_2 in children with asthma [48]. These effects may manifest as early as the preschool age. In one study in urban Baltimore, asthmatic children (ages 2–6) who spent most of their time in the home had increased respiratory symptoms and rescue medication use in response to increases in $PM_{2.5}$ and $PM_{2.5–10}$ [50]. Such studies have real implications for the development of appropriate interventions aimed at reducing the health impact of airborne pollution in children.

There are multiple reasons why young children may disproportionately bear the brunt of air pollution. For example, children have greater indoor exposures because of increased time spent at home, higher respiratory rates that lead to greater intake of pollutants per unit body weight, and higher levels of physical activity and exploratative tendencies. They are also undergoing ongoing lung growth and development and have young immune systems, characteristics that may render them more susceptible to airway injury [51, 52]. The damage sustained at these vulnerable times also may have more permanent effects, as lung development continues into adulthood.

At the other end of the spectrum are the elderly, who may also spend a significant time indoors. Studies dedicated to the differential effects of air pollution in persons of older age are limited and use a variety of age cutoffs to define their populations. Individual examination of these studies reveals conflicting results with regard to associations between PM exposure and respiratory health effects. However, meta-analysis performed with a subset of 23 studies looking at older populations did find that a 10 $\mu g/m^3$ increase in PM_{10} exposure led to higher increases in mortality (0.64

% vs. 0.34 % increase in risk of death) among older compared to younger subgroups [53]. The reasons for such effect modification are not clear but may include elements such as comorbid conditions, nutritional status, or access to healthcare which heighten the susceptibility and vulnerability of elderly persons to air pollution.

Place

Thus far, we have discussed the disparities that pertain to environmental air quality exposure across subpopulations stratified by SES, race, gender, and age, and the dividing lines between each of these categories are often indistinct. Yet another potential disparity in air quality exposure may lie between urban and rural populations, each of which has distinct characteristics with regard to the elements such as composition of their inhabitants, the concentration of stationary and mobile emission sources, and the accessibility of healthcare services.

One global example of the rural–urban divide is tied to biomass fuel burning, which more heavily impacts rural populations. For example, in China, one study comparing cooks in rural to urban areas found that concentrations of PM_{10} were 64 % higher in rural kitchens [54]. These indoor levels translated to the personal exposure of the cooks, who inhaled $PM_{2.5}$ levels 5.4 times greater than cooks from urban areas. Possible reasons for this differential are the use of cleaner fuels such as liquid petroleum gas (LPG) or mixed fuels in wealthier urban areas instead of biomass, as well as the longer cooking times required to gather and cook with biomass fuel used in rural areas [54].

A reversal of these urban–rural disparities in air pollution may occur in industrialized nations, where individuals living in urban environments may have greater risk of pollution exposure because of dense population, proximity to industrial power plants and/or manufacturing stations, and congested traffic patterns prone to idling. Moreover, other factors related to urbanization may affect pollution exposure and health effects, including the high percentage of racial/ethnic minority and low-income populations, lifestyles that shape activity level and diet, social stresses, access to medical care, and co-exposure to other pollutants and allergens within urban neighborhoods [21].

In their 2001 workshop report of health disparities of urban air pollution, The American Lung Association reviewed the evidence for environmental inequalities within metropolitan areas and highlighted the need for a coordinated research agenda to address the needs of these communities going forward [55]. Specific recommendations to identify the mechanisms by which urban exposures lead to adverse health effects—especially in those subpopulations with disproportionate burdens of disease—included improved air quality and exposure measurements, research on chronic and acute health effects along with intervention research, integration of community-based research (CBR), and use of public policy efforts to manage these inequities [55]. Now may be the time to assess the progress we have made since

these recommendations and to reexamine the disparities in air pollution that still exist in urban neighborhoods.

Summary and Conclusions

In the more than half a century since the Great London Smog heightened our awareness of the tangible health effects of air pollution, a greater appreciation for the sources, components, and dynamics of toxins in the air has grown from the extensive research efforts of the scientific community. Inequalities across exposures and susceptibilities in global subpopulations have resulted in disproportionate health effects from pollution exposures. Socioeconomic status, race, gender and sex, age, and geographic boundaries, though often overlapping, each uniquely modify the human experience of pollution exposure and challenge both our understanding of its ill effects as well as our abilities to mitigate its consequences.

Broadly, the evidence supports that people in poverty, racial minorities, women, children, the elderly, and developing rural and inner-city inhabitants suffer a disproportionate degree of the adverse effects of poor air quality. These patterns are not wholly the result of unequal distribution of exposures but are also of coincident biological and social susceptibilities unique to these subgroups. This fundamentally violates the tenets of environmental justice that uphold that no one group should bear an excessive share of the pollution burden, and the significant and lifelong health impacts that ensue from these exposures elevate this violation to a matter of human rights for vulnerable populations.

However, no one group can be "safe" or immune to the far-reaching nature of outdoor pollution as it sweeps across continents, nor to the toxins emerging from the indoor environments that we create in our own homes in which we purposefully seal ourselves. Yet the solution, as in so many public health problems, does not easily rely on simply accelerating technology, as both industrialized and "underdeveloped" regions of the world face the issues of air pollution in parallel, often with further advancements introducing new brands of poisons. Rather, we must use the knowledge accumulated in research and the roads of public advocacy paved through government and community activity to create dedicated action plans that prevent the release of environmental pollutants to begin with, as well as implement interventions that attempt to reverse the destruction already incurred. In these efforts, we will ultimately be serving and protecting *all* from ongoing global threat.

References

1. Bell ML, Davis DL. Reassessment of the lethal London fog of 1952: novel indicators of acute and chronic consequences of acute exposure to air pollution. Environ Health Perspect. 2001;109 Suppl 3:389–94.
2. Davis DL, Bell ML, Fletcher T. A look back at the London smog of 1952 and the half century since. Environ Health Perspect. 2002;110(12):A734–5.
3. Arbex MA, Santos Ude P, Martins LC, Saldiva PH, Pereira LA, Braga AL. Air pollution and the respiratory system. J Bras Pneumol. 2012;38(5):643–55.
4. Health effects of outdoor air pollution. Committee of the environmental and occupational health assembly of the American Thoracic Society. Am J Respir Crit Care Med. 1996;153(1):3–50.
5. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. J Med Toxicol. 2012;8(2):166–75.
6. Hansel NN, Breysse PN, McCormack MC, et al. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. Environ Health Perspect. 2008;116(10):1428–32.
7. Hansel NN, McCormack MC, Belli AJ, et al. In-home air pollution is linked to respiratory morbidity in former smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(10):1085–90.
8. Liu J, Lewis G. Environmental toxicity and poor cognitive outcomes in children and adults. J Environ Health. 2014;76(6):130–8.
9. Brunekreef B, Holgate ST. Air pollution and health. Lancet. 2002;360(9341):1233–42.
10. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of cohorts for air pollution effects (ESCAPE). Lancet Oncol. 2013;14(9):813–22.
11. Paulin LM, Diette GB, Scott M, et al. Home interventions are effective at decreasing indoor nitrogen dioxide concentrations. Indoor Air. 2014;24(4):416–24.
12. Klepeis NE, Nelson WC, Ott WR, et al. The national human activity pattern survey (NHAPS): a resource for assessing exposure to environmental pollutants. J Expo Anal Environ Epidemiol. 2001;11(3):231–52.
13. McCormack MC, Breysse PN, Hansel NN, et al. Common household activities are associated with elevated particulate matter concentrations in bedrooms of inner-city Baltimore pre-school children. Environ Res. 2008;106(2):148–55.
14. Sood A. Indoor fuel exposure and the lung in both developing and developed countries: an update. Clin Chest Med. 2012;33(4):649–65.
15. Ryan PH, Reponen T, Simmons M, et al. The impact of an anti-idling campaign on outdoor air quality at four urban schools. Environ Sci Process Impacts. 2013;15(11):2030–7.
16. Kinsey JS, Williams DC, Dong Y, Logan R. Characterization of fine particle and gaseous emissions during school bus idling. Environ Sci Technol. 2007;41(14):4972–9.
17. Briggs D. Environmental pollution and the global burden of disease. Br Med Bull. 2003;68:1–24.
18. Gudmundsson G. Respiratory health effects of volcanic ash with special reference to Iceland. A review. Clin Respir J. 2011;5(1):2–9.
19. Deguen S, Zmirou-Navier D. Social inequalities resulting from health risks related to ambient air quality—a European review. Eur J Public Health. 2010;20(1):27–35.
20. Brulle RJ, Pellow DN. Environmental justice: human health and environmental inequalities. Annu Rev Public Health. 2006;27:103–24.
21. Makri A, Stilianakis NI. Vulnerability to air pollution health effects. Int J Hyg Environ Health. 2008;211(3–4):326–36.
22. Mackenbach JP, Stirbu I, Roskam AJ, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med. 2008;358(23):2468–81.

23. Wright RJ, Subramanian SV. Advancing a multilevel framework for epidemiologic research on asthma disparities. Chest. 2007;132(5 Suppl):757S–69.
24. Davies M, Adshead F. Closing the gap in a generation: health equity through action on the social determinants of health. An international conference based on the work of the commission on social determinants of health, 6–7 November 2008, London. Glob Health Promot. 2009;Suppl 1:7–8; 95–6; 108–9.
25. Richardson EA, Pearce J, Tunstall H, Mitchell R, Shortt NK. Particulate air pollution and health inequalities: a Europe-wide ecological analysis. Int J Health Geogr. 2013;12:34.
26. Miranda ML, Edwards SE, Keating MH, Paul CJ. Making the environmental justice grade: the relative burden of air pollution exposure in the United States. Int J Environ Res Public Health. 2011;8(6):1755–71.
27. Gray SC, Edwards SE, Miranda ML. Race, socioeconomic status, and air pollution exposure in North Carolina. Environ Res. 2013;126:152–8.
28. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the United States. Environ Health Perspect. 2012;120(12):1699–704.
29. Sacks JD, Stanek LW, Luben TJ, et al. Particulate matter-induced health effects: who is susceptible? Environ Health Perspect. 2011;119(4):446–54.
30. Lopez R. Segregation and black/white differences in exposure to air toxics in 1990. Environ Health Perspect. 2002;110 Suppl 2:289–95.
31. Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities. Environ Health Perspect. 2006;114(8):1150–3.
32. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS Data Brief. 2012;94:1–8.
33. Nachman KE, Parker JD. Exposures to fine particulate air pollution and respiratory outcomes in adults using two national datasets: a cross-sectional study. Environ Health. 2012;11:25.
34. Gold DR, Rotnitzky A, Damokosh AI, et al. Race and gender differences in respiratory illness prevalence and their relationship to environmental exposures in children 7 to 14 years of age. Am Rev Respir Dis. 1993;148(1):10–8.
35. Clougherty JE. A growing role for gender analysis in air pollution epidemiology. Environ Health Perspect. 2010;118(2):167–76.
36. Mortimer K, Gordon SB, Jindal SK, Accinelli RA, Balmes J, Martin 2nd WJ. Household air pollution is a major avoidable risk factor for cardiorespiratory disease. Chest. 2012;142(5): 1308–15.
37. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374(9691):733–43.
38. Kodgule R, Salvi S. Exposure to biomass smoke as a cause for airway disease in women and children. Curr Opin Allergy Clin Immunol. 2012;12(1):82–90.
39. Perez-Padilla R, Regalado J, Vedal S, et al. Exposure to biomass smoke and chronic airway disease in Mexican women. A case-control study. Am J Respir Crit Care Med. 1996; 154(3 Pt 1):701–6.
40. Hu G, Zhou Y, Tian J, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest. 2010;138(1):20–31.
41. Rinne ST, Rodas EJ, Rinne ML, Simpson JM, Glickman LT. Use of biomass fuel is associated with infant mortality and child health in trend analysis. Am J Trop Med Hyg. 2007;76(3): 585–91.
42. Sreeramareddy CT, Shidhaye RR, Sathiakumar N. Association between biomass fuel use and maternal report of child size at birth—an analysis of 2005–06 India demographic health survey data. BMC Public Health. 2011;11:403.
43. Ebisu K, Bell ML. Airborne PM2.5 chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States. Environ Health Perspect. 2012;120(12):1746–52.
44. Ritz B, Qiu J, Lee PC, et al. Prenatal air pollution exposure and ultrasound measures of fetal growth in Los Angeles, California. Environ Res. 2014;130:7–13.

45. Pedersen M, Giorgis-Allemand L, Bernard C, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med. 2013;1(9):695–704.
46. Shah PS, Balkhair T, Knowledge Synthesis Group on Determinants of Preterm/LBW births. Air pollution and birth outcomes: a systematic review. Environ Int. 2011;37(2):498–516.
47. Anderson ME, Bogdan GM. Environments, indoor air quality, and children. Pediatr Clin North Am. 2007;54(2):295–307, viii.
48. Li S, Williams G, Jalaludin B, Baker P. Panel studies of air pollution on children's lung function and respiratory symptoms: a literature review. J Asthma. 2012;49(9):895–910.
49. Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. Environ Health Perspect. 2010;118(4):449–57.
50. McCormack MC, Breysse PN, Matsui EC, et al. In-home particle concentrations and childhood asthma morbidity. Environ Health Perspect. 2009;117(2):294–8.
51. Schwartz J. Air pollution and children's health. Pediatrics. 2004;113(4 Suppl):1037–43.
52. Le Cann P, Bonvallot N, Glorennec P, Deguen S, Goeury C, Le Bot B. Indoor environment and children's health: Recent developments in chemical, biological, physical and social aspects. Int J Hyg Environ Health. 2011;215(1):1–18.
53. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. Am J Epidemiol. 2013;178(6):865–76.
54. Jiang R, Bell ML. A comparison of particulate matter from biomass-burning rural and non-biomass-burning urban households in northeastern China. Environ Health Perspect. 2008;116(7):907–14.
55. American Lung Association. Urban air pollution and health inequities: a workshop report. Environ Health Perspect. 2001;109 Suppl 3:357–74.

Chapter 4
Health Disparities in Occupational Exposures

Kenneth D. Rosenman

Key Points

- Respiratory occupational health disparities have occurred from the overrepresentation of minorities in hazardous industries and job titles with respiratory toxins.
- Known respiratory occupational health disparities have been identified from medical studies and high profile events as there is no ongoing nationwide surveillance system that is tracking work-related health disparities.
- Minorities continue to be overrepresented in particular industries and occupations despite the cessation of overt discriminatory hiring practices.
- The addition of occupation and industry to health surveys and race/ethnicity to occupational injury and illness surveillance systems is needed to provide ongoing evaluation.

"When the white man had a job, his job wasn't molding and shaking out. He had a job like setting cores. You couldn't hardly find a one that shake out [foundry department with the highest silica dust levels]*."* (Quote from a black retired Michigan foundry worker describing work conditions from the mid-1950s to the mid-1970s) (see Fig. 4.1).

K.D. Rosenman, M.D. (✉)
Department of Medicine, Michigan State University, East Lansing, MI, USA
e-mail: Ken.Rosenman@hc.msu.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_4

Fig. 4.1 African-American foundry worker preparing to pour molten metal at a foundry in Minnesota. Photo by David Parker, MD

Introduction

Federal and state governmental programs to address health disparities generally have not included addressing occupational health disparities as part of their mission [1]. However, for the first time in 2013, the Centers for Disease Control and Prevention (CDC) report on health disparities contained two chapters related to occupational health which focused on disparities in work-related nonfatal injuries and illnesses and on work-related fatal injuries [2]. The long-standing omission in addressing occupational health disparities has occurred despite the many examples in the medical literature of a disproportionate occurrence of work-related injuries and illnesses in minority and immigrant populations [3–7], the estimated economic costs of occupational injuries and illnesses in low-wage workers of $15 billion for medical care and another $24 billion for lost productivity [8], and a history of tragedies among minority and immigrant workers. An example of a well-known occupational tragedy in labor history was the 1911 Triangle shirtwaist factory fire in New York City when 146 predominantly female immigrant textile workers died [3]. This chapter will focus on health disparities in the USA as they relate to occupational respiratory exposures and illnesses.

Most respiratory-related occupational health disparities are related to the overrepresentation of minorities in hazardous industries and job titles/assignments that involve increased exposure to respiratory toxins [9–14]. Additionally, there has

been incomplete penetration of occupational health and safety interventions to certain worker populations due to barriers created by social, cultural, and economic issues including language, literacy, and marginal economic status [15–17]. Examples of the latter would be migrant farm workers or construction day laborers, who are predominately Hispanic. The aggregation of lower socioeconomic and immigrant populations in certain industries and occupations is an ongoing issue that suggests that historically well-documented occupational respiratory health disparities have the potential to continue in the future. The uneven distribution of race and ethnicity by occupations in Michigan is described later in the chapter as an illustration of job placement throughout the USA.

Although work-related health disparities have been recognized through high profile events and research studies, there is no ongoing nationwide surveillance system to track work-related health disparities [18]. Race and ethnicity data from the Bureau of Labor Statistics annual Survey of Occupational Injuries and Illnesses (SOII) are very limited and not summarized in official publications because employer reporting of these data elements is voluntary and is missing in 37 % of submitted records [19]. Additionally, most workers compensation data systems are not useful for tracking disparities by race and ethnicity because the national standard for recording worker compensation claims that is used by 80 % of state systems does not have data elements that cover race or ethnicity [20].

A limited number of states (23) have their own occupational health surveillance system and even fewer (California, Massachusetts, Michigan, New Jersey, and New York) conduct any surveillance for occupational respiratory disease, which is for the most part limited to work-related asthma. At this time, Michigan is the only state that conducts surveillance for all occupational lung diseases. Although limited in their scope, these state programs are capable of collecting data about race and ethnicity through access to demographic information in hospital discharge records, health care provider reports, and death certificates.

This chapter will review the overrepresentation of racial and ethnic minority workers in the most hazardous occupations and industries, providing specific examples of increased respiratory morbidity and mortality in minority workers due to disparities in exposure to chromates, coke oven emissions, cotton dust, radiation, and silica using information from epidemiologic studies and public health surveillance data [9–14].

Chromates

Beginning in the 1930s, cases of lung cancer among chromate production workers were reported in the German medical literature. In the 1950s, the United States Public Health Service (USPHS) studied the workers at all seven US production facilities (four in New Jersey, one in New York, one in Ohio, and one in Maryland) where chromates and bichromates were made from chromite ore [9]. USPHS found that black males constituted 37 % of the total workforce, and most black workers

came from the South. For example, less than 4 % of the black workers in the four New Jersey facilities were born in that same state. The vast majority (86 %) of black workers in the chromate industry were employed at the two largest facilities, where they represented 46 % and 37 % of the workforce, respectively. The proportion of white workers was much lower in the production areas (mill room 67 %, kiln room 53 %, primary leach and residue drying 29 %, liquor room 71 %, and special processes 68 % white) compared to areas of lower exposure, such as maintenance (93 % white) and office, laboratory, and outside yard workers (79 % white).

The USPHS study found that respiratory morbidity and mortality were high in all chromate workers, but notably, black workers had greater risk than white workers in these facilities [9]. For example, the prevalence of nasal perforation, which has been associated with chromate work since the early 1800s, was higher in black workers (76.6 %) compared to white workers (49.3 %). Moreover, chromate workers overall demonstrated a 29-fold increased risk of death from respiratory cancer, but separated by race, the risk of lung cancer was increased 80-fold in black workers compared to only 15-fold in white workers. This is due to the production of hexavalent chromium compounds, which are known human carcinogens, during conversion of chromite ore to chromates. The increased risk of respiratory cancer death in blacks compared to whites was particularly notable because the prevalence of smoking among white and black workers was similar (81 % vs. 84 %,), the prevalence of heavy smoking was higher among whites (32 % vs. 12 %), and a higher proportion of white workers had a longer duration of exposure (proportion of white workers with ≥20 years employment was 21.8 % compared to 10.2 % among black workers). However, hexavalent chromium exposures were highest in those areas with a higher percentage of black workers (kiln, leach, and liquid areas). There is no discussion in the USPHS report describing how workers were assigned jobs in these facilities. In the early 1990s, a follow-up study was conducted examining the vital status of the New Jersey portion of the cohort. For workers with more than 20 years since first exposure and work duration of at least 20 years, the proportionate cancer mortality ratio for lung cancer was 3.08 (95 % CI 1.13–6.71) in black workers compared with 1.94 (95 % CI 1.15–3.06) in white workers [21]. Follow-up of these former workers is still ongoing although the facilities in New Jersey have closed.

Chromite ore continues to be imported into the USA, and the USA continues to be a major producer of chromium products with the largest facilities in Indiana, Louisiana, Massachusetts, Nebraska, Ohio, Pennsylvania, South Carolina, Texas, and Wisconsin.

Coke Oven Emissions

Metallurgical coke is used in the process of making iron. Iron ore, limestone, and coke are added to the blast furnace to produce iron, which can be further processed into steel. By the 1930s, most coke was made in "by-product" ovens from coal (Fig. 4.2). Coke is the residue of coal after the volatile components of coal are removed during

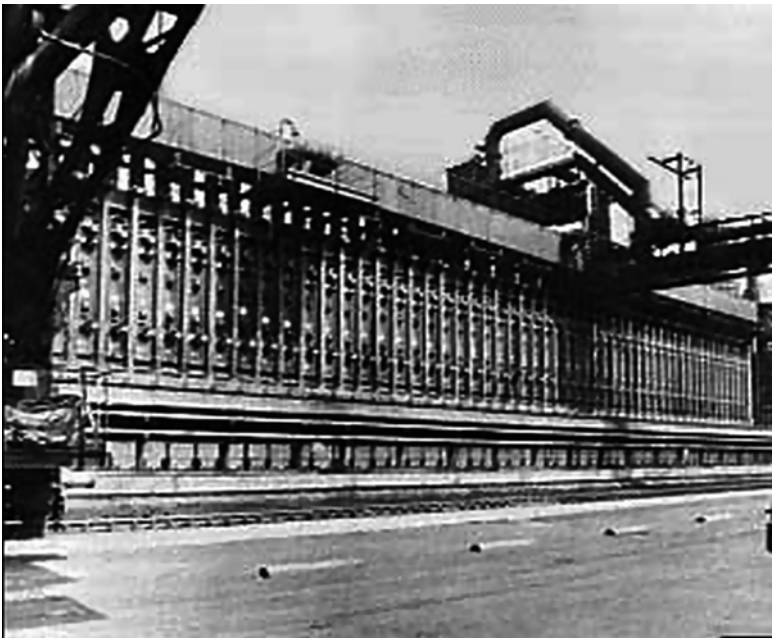

Fig. 4.2 Pusher side of a by-product coke oven battery Courtesy of "The Making, Shaping and Treating of Steel." Courtesy association of iron and steel Engineers

6–20 h of heating at temperatures from 700 to 1200°C. The tars, oils, and chemicals removed from the coal during the heating process are recovered and sold. Coal tar pitch volatiles released during the heating process are known human carcinogens [22] and contain polycyclic aromatic hydrocarbons such as anthracene and benzo(a) pyrene, aromatic compounds such as benzene and β-napthylamine, and metals such as arsenic and chromium. Coke oven emissions also include gases such as nitric oxides and sulfur dioxide, and emissions are highest in the work areas on the top of the coke ovens.

In 1970, an important study was published that examined mortality by specific work area in 58,828 steel workers employed at seven facilities, including two with coke manufacturing, in Allegheny County, Pennsylvania [23]. Race was identified from personnel files as white and non-white. All-cause mortality among white coke workers was not increased compared to the general population, but there was a 22 % increase in the risk of death among non-white coke workers. Similarly, there was no increase in risk of overall cancer death among white coke workers, but among non-white coke workers, the risk of cancer death was double that which was observed in the general population.

Coke plant workers worked in three distinct areas: (1) handling coal; (2) loading and unloading the coke ovens; and (3) processing the by-products removed from the coal. Of the total workforce, 89 % of non-white workers versus 32 % of white

workers participated in loading and unloading the coke ovens. Non-white workers made up 61 % of the coke oven workforce but only 8 % of the non-oven workforce. Across the entire coke plant workforce, there was a 75 % increase in the risk of respiratory cancer compared to the general population, but this was due to increased risk among non-white workers. White coke plant workers had less respiratory cancer than expected, while non-white coke plant workers had an increased risk of respiratory cancer death [10]. These findings reflect the work area location of non-white coke plant workers in the coke oven area. Further characterizing the coke oven workers as "topside" versus "never worked topside" found that non-white workers made up 73.5 % of the topside workforce and had 10.8-fold increased risk of respiratory cancer. Although there was a fivefold increased risk of respiratory cancer among the fewer number of white topside workers, with one death compared to 0.2 expected, no statistical tests were performed in this study where there were less than five deaths.

In a subsequent publication, the study was expanded to include coke plant workers from ten other facilities in the USA and Canada. Non-whites made up 70.4 % of topside coke oven workers in this larger cohort. The highest risk for cancer of the lung, bronchus, and trachea continued to be among non-white topside workers with a 7.68-fold significantly increased risk compared to non-white, non-coke plant workers [24]. Follow-up of the vital status of this cohort through 1982 found risk of respiratory cancer was 1.59-fold higher (95 % CI 1.19–2.12) for white workers and 2.12-fold higher (95 % CI 1.70–2.84) for non-white workers among all coke plant workers compared to non-coke plant workers [25]. Topside workers continued to have the highest risk of death from respiratory cancer, demonstrating 4.25-fold higher risk (95 % CI 2.91–7.14) after working 10–14 years topside, 4.45-fold higher risk (95 % CI 2.79–7.56) after working 14–19 years topside, and 4.34-fold higher risk (95 % CI 2.89–6.97) after working 20 or more years topside compared to non-coke plant workers [25].

In 1966, coke oven exposure assessments were performed that measured coal tar pitch volatiles, thereby allowing for dose–response studies [26, 27]. Reinforcing the notion that topside jobs are associated with the greatest exposure, the average concentration of coal tar pitch volatiles for topside jobs was 3.15 mg/m^3, which was 3.6-fold higher than the average level for side oven jobs and dramatically higher than the Occupational Safety and Health Administration's current permissible exposure limit of 0.2 mg/m^3. In further support of this, measurements of polycyclic aromatic hydrocarbons in the air and in worker urine samples from multiple coke ovens in different countries in the 1980s and 1990s demonstrated consistently higher exposure levels to topside workers [22] (IARC, 2005). Estimates of cumulative exposure to coal tar pitch volatiles among non-white workers, consistent with their more frequent assignment to topside jobs, were higher than white workers [26] (see Table 4.1). The risk for lung cancer mortality between non-white and white workers has been reported to be similar when duration of employment and job location topside was taken into account [28]. The disparity in lung cancer mortality observed is thus attributed to the overrepresentation of non-whites in topside jobs. A 1973 affirmative action ruling at a steel plant in Maryland documented ongoing

Table 4.1 Cumulative exposure to coal tar pitch volatiles among non-white and white coke oven workers based on sampling performed in 1966

Cumulative exposure (mg/m^3-months)	Non-white workers		White workers	
	#	%	#	%
<200	865	(32.3)	970	(49.0)
200–499	1042	(38.9)	807	(40.8)
500–699	422	(15.7)	140	(7.1)
700+	353	(13.2)	62	(3.1)
Total	2682		1979	

Data obtained from [26]

discriminatory job placement in this industry with blacks making up 75–100 % of the workforce of some departments including coke ovens and 0 % of other departments such as pipefitting or machining [29].

From 1950 to 1968, the lung cancer mortality rate for non-white males in Allegheny County was 28 % higher than that in white males. This is in contrast to the fact that non-white males had a slightly lower mortality rate for lung cancer than white males during the same time period at the national level [29]. The increased risk from a given work area in a given industry is presumably one factor explaining this difference between Allegheny County and the national rates. It is example of how the increased risk of cancer from an occupational exposure may affect local geographic rates when that industry workforce makes up a large enough proportion of the population in a geographic area [30].

Cotton Dust

Exposure to cotton in textile mills is associated with acute respiratory symptoms and the development of chronic bronchitis and COPD, particularly with long-term work in high dust areas such as opening bales, "picking" (a process that is no longer necessary in modern textile mills that used to prepare the cotton lint for carding), and carding (separation and alignment of fibers). In 1973, a survey that measured respiratory symptoms and pulmonary function was conducted in 6432 workers at 14 US textile plants [12]. Black men had a higher prevalence of acute symptoms consistent with byssinosis (5.5 % vs. 3.6 % in white men). Among the 165 cases of byssinosis identified, 64 % of the cases worked in the high dust work areas, where only 12 % of the overall textile mill workforce was located. Blacks made up 64.5 % of the workforce in the high dust areas, which was much greater than their overall workforce prevalence of 34.4 %. Despite the fact that blacks had a shorter duration of work, chronic bronchitis prevalence was similar between blacks and whites. Moreover, blacks had lower pulmonary function results than whites, with workers in the dustier area having the lowest results. Data on cigarette smoking was not provided by race, but it was noted, that there were less heavy smokers in the dustier

work areas, where the workforce was 64.5 % black. Much of this industry has now moved overseas with reports of respiratory disease among cotton textile workers now being reported from China, India, Pakistan, and Turkey.

Radiation

Significant uranium mining began in the USA during World War II. The mines were predominately located in the southwest on the Colorado Plateau where the four states of Arizona, Colorado, New Mexico, and Utah abut. In this region, major deposits of uranium were identified on the Navajo Reservation. Four centers of mining and milling were established there, and there are an estimated 1000 abandoned shafts on the reservation [31]. Mining was the primary industry offering job opportunities for most Navajo individuals, and the peak years of mining occurred from 1948 to 1969. Although the risk of lung cancer among uranium miners was first recognized in Europe as early as 1879 and was made compensable in Europe in the 1930s, there were no regulatory standards for limiting radiation exposure during the peak years of mining on the Navajo reservation [32]. Navajo miners were paid minimum wage, and they worked underground blasting, building wooden supports, digging blasted rock (muckers), transporting ore, and milling ore. Foremen were white and thus did not spend as much time underground.

Mining dust contains radon progeny which produce alpha particles responsible for the increased lung cancer risk. The nomenclature for expressing radon progeny exposure is based on working levels. A working level (WL) is the amount of radon progeny in a liter of air that releases a specified amount of alpha radiation. Exposure to a WL for 170 h (the average number of work hours in a month) equals a working level month (WLM). Background levels of radon progeny from radon contamination in homes cause the average person in the general population to have a lifetime exposure of 10–20 WLM. In contrast, WLM exposures in miners with lung cancer ranged from 465 to 16,467 [33]. Current workplace regulations allow up to 4 WLM/year or 160 WLM over a 40 year working lifetime.

From 1969 to 1982, 72 % of the lung cancer cases among Navajo men in the New Mexico Cancer Registry had been employed by a uranium mine versus 0 % of controls in a matched case–control study [34]. This corresponds to an infinite odds ratio with a 95 % CI lower limit of 14.4. Thirty-eight percent of the uranium miners with lung cancer in this study were nonsmokers, while the other 62 % of Navajos with lung cancer averaged only one to three cigarettes per day. Consistent with the low smoking burden in the case control study of Navajo miners with lung cancer, a survey of Navajo miners showed low smoking prevalence (41 % ever smokers) and low cigarette consumption among active smokers [31]. An extension of the New Mexico cancer registry case–control study until 1993 continued to find a high percentage (67 %) of lung cancer in Navajo men to be attributable to past work in the uranium mines. This later study was able to calculate an odds ratio since some controls in this later study had worked in the uranium mines; the investigators found an odds

ratio of 28.6 (95 % CI 13.2–61.7) compared to matched Navajo men with non-respiratory cancer [32]. Surveys of white miners have found appreciably higher cigarette smoking rates, with only 18 % of white miners having never smoked versus 59 % in the Navajo miners [35]. The joint effect of cigarette smoking and radon progeny exposure is synergistic [36]. Despite the lower smoking rates in Navajo miners, lung cancer risk between white and Navajo miners were similar and are indicative of higher radon progeny exposure in Navajo miners [14, 35].

A cross-sectional study of miners who participated in the New Mexico Miners Outreach Program found that Navajos who had worked in the uranium mines demonstrated an increased risk of chronic obstructive pulmonary disease (COPD), low lung function (FEV1), and radiologic evidence of pneumoconiosis in relation to years worked [37]. However, this was not true of white miners who had worked in uranium mines. In this study, 73 % of Navajo miners had never smoked cigarettes, and those who had smoked cigarettes averaged 6.4 cigarettes per day. In contrast, only 22 % of white uranium miners had never smoked cigarettes, and among those who had the average were 20.3 cigarettes per day. Thus, the increased risk of respiratory disease in relation to work only occurred among Navajo miners, despite decreased cigarette smoking among Navajo compared to white uranium miners.

Rubber Workers

Mortality of workers from a large rubber tire manufacturing plant in Akron, Ohio, was examined between 1964 and 1972. Study investigators identified a greater than twofold difference in the proportion of whites and blacks in different occupations with blacks being more likely to have worked in high exposure occupations such as compounding and mixing (27 % of blacks vs. 3 % of whites had worked in this occupation). There was an increased age-standardized risk ratio of lung cancer of 1.4 (99.9 % CI 1.1–2.0) in the compounding and mixing area compared to local county or national rates [11], but this risk was only significantly increased for black workers in the area. This latter difference was “clearly influenced by the racial composition of the workforce in that work area” [11]. Potential exposures to carcinogens in this work area would have included asbestos and silica, which are also known to cause chronic lung disease, as well as multiple solvents. Disparities in respiratory health related to this industry are likely ongoing today, as there are approximately 40 rubber tire manufacturing facilities in the USA and appreciably more worldwide.

Silica

Silicon in combination with oxygen, silica (silicon dioxide) is one of the most common constituents of the earth’s crust. Mining for any mineral or tunneling will cause generation of respirable dust that will contain varying percentages of silica

depending on the underlying geology of the particular rock formation. Silica is widely used in foundries in the production of metal products and the production of ceramic products such as sinks and toilet bowls, and there is also risk of silica exposure during abrasive blasting, and more recently in the process of fracking as part of oil and gas drilling.

Example #1: Hawk's Nest, West Virginia

In March 1930, dam construction on the New River began at Hawk's Nest, West Virginia, and this included boring a three mile water tunnel through Gauley Mountain to power a new power plant at Gauley Bridge (see Fig. 4.3). Tunnel construction required drilling through sandstone that was over 99 % silica. Despite the dustiness and high silica content of the rock being tunneled, water suppression to keep dust levels down was not used because of the rapid speed of drilling that was required to meet the 17.5 month contract deadline for completion of the tunnel. It is estimated that the total number of workers at the job site was about 5000, of whom 2500 worked underground in the tunnel. Turnover was high with an average length

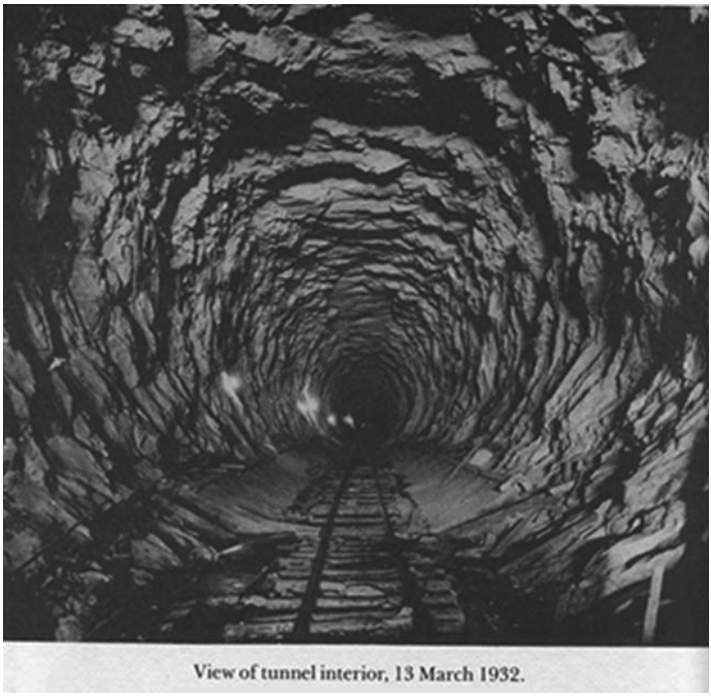

Fig. 4.3 Interior of Hawk Mountain tunnel in 1932. Courtesy West Virginia archives and history

of employment of 15 weeks. There were 600 tunnel workers at any one time. Silica exposure was highest for underground workers, which included 75 % of African-American workers versus only 44 % of white workers. White workers who did work underground were more likely to be foreman or heavy equipment operators, whereas African Americans were drillers, muckers (who hauled away rock and debris), and driller assistants. There were two 10-h work shifts each day with ongoing work 6 days a week. During each shift, drilling was performed to set the dynamite (600–800 lb per charge), the charge was set, and then the rock and debris were removed after the explosion. Eighteen deaths (5 whites and 13 blacks) occurred from acute traumatic injuries, and a much larger number of workers died from respiratory disease. Sixty-five percent of the overall workforce was composed of African-American men who came from southern states to work at the site. Their migrant status and racism are factors that may have delayed the initial recognition and response to addressing the epidemic of work-related respiratory disease that occurred. Other factors that have been identified that contributed to the delay in response include: (1) high worker turnover with workers returning to their home states when they became sick, (2) slow reporting on the part of local newspapers with respect to worker deaths, (3) fear and intimidation on the worksite that limited reporting, and (4) attribution of deaths to poor nutrition and inability of African Americans from southern states to tolerate cold weather.

Within a few years after the tunnel was completed, the related respiratory epidemic was recognized as silicosis that occurred in response to silica dust exposure during the tunneling operation. Unfortunately, no accurate count of the number of workers who died or developed silicosis is available. During congressional hearings that were held 5 years after completion of the tunnel in 1936, a senator stated there were 2000 deaths. There was also testimony from one funeral home director indicating he was paid to dig 169 unmarked graves. In support of this, highway construction records from a 1972 West Virginia Department of Transportation contract documented removal of 63 unmarked graves during construction of a nearby road. For the entire tunneling project, the official death toll from the company was 109, including the traumatic deaths. However, by 1933, worker compensation suits were filed by 336 individuals.

The best estimate of deaths from silicosis was derived in 1986 [13]. This estimate used county death records and determined the excess respiratory deaths from 1931 to 1937 that occurred in Fayette County, where Hawk's Nest was located, in comparison to adjoining West Virginia counties and extrapolated the number of migrant worker deaths that were not reported in the county. Cherniak's calculation was based on 1213 workers, 291 whites and 922 blacks, who worked at least 2 months underground and were considered to be at the highest risk of developing silicosis. The total number of workers estimated to have died from silicosis was 764, including 581 (63 %) of the 922 African-American workers and 183 (62.8 %) of the 291 white workers who worked 2 or more months underground. Typically, silicosis related to work exposure in foundries or mines develops after 20 or more years of exposure, but for the limited number of identified workers with available

medical records from Hawk's Nest, it appears the high silica exposure in the tunnel resulted in a short time to development of respiratory disease, with workers dying within months and a few years of exposure due to acute silicosis (pathology similar to alveolar proteinosis) and accelerated silicosis (same pathology as chronic silicosis but rapid onset). No long-term follow-up was conducted on this workforce, and there is no data on the incidence of chronic silicosis or the development of tuberculosis. Presumably, this was already a population with an increased prevalence of tuberculosis, and active tuberculosis is more common and virulent in individuals with a history of silica exposure [38].

Example #2: Foundries

Ford Motor Company was the largest employer of black auto workers prior to World War II, as they started to hire a large number of African-Americans in 1918. Other auto manufacturers did not begin to hire blacks in appreciable numbers until the labor shortages of World War II. For example, the largest grey iron foundry in the USA located in Muskegon, Michigan, sent personnel managers to the south during World War II and paid black workers to move north to work in their foundry. Ford paid black and white workers the same wage but placed blacks in the undesirable, hot, and more dangerous foundry jobs where the quit rates of white workers had been high [39]. Given the lack of alternatives for black workers and the relatively good pay, quit rates from foundry jobs by blacks were low, and foundries became known as the "black departments." The consequence of the concentration of blacks in foundries is reflected in the current statistics on the incidence of silicosis. In Michigan, 40 % of individuals with silicosis are African-American, although African-Americans only make up 14.3 % of the Michigan population [40]. The annual average incidence rate of silicosis among African-American males (8.8 cases per 100,000) is 5.5 times higher than that of white males (1.6 cases per 100,000). The rates within specific Michigan counties range between 2 and 366 times higher for African-American males than the rates for white males [40].

Significant racial disparity in silica exposure in foundries is documented from a study of a foundry in another Midwestern state [41]. In a cross-sectional study of current and retired workers, the prevalence of silicosis was 8.3 % among blacks and 4.0 % among whites. This higher prevalence of silicosis among African-Americans was found despite the fact that white and black workers had a similar distribution of duration of work, which is a common surrogate measure often used to estimate workplace exposures (see Fig. 4.4). The cause of the higher silicosis prevalence in black workers was their higher levels of silica exposure despite working the same number of years as white workers (see Fig. 4.5). This later determination was possible because of a detailed job exposure matrix that was developed during a review of industrial hygiene sampling results over many years, which documented that African-Americans had jobs with higher silica exposure [42]. In analyses control-

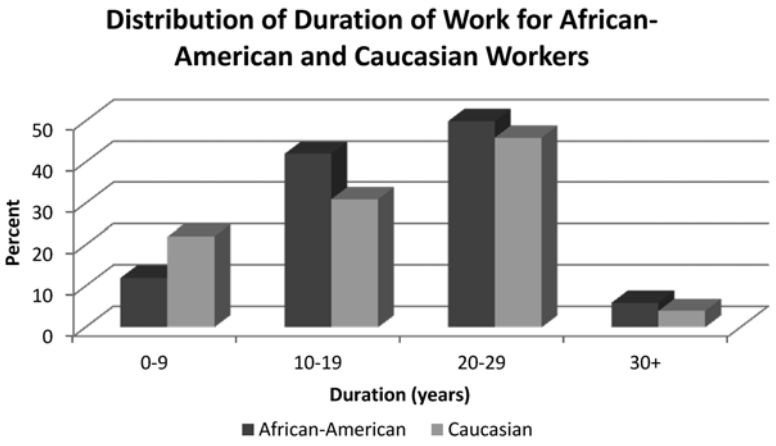

Fig. 4.4 Duration of work for African-American and Caucasian workers at a gray iron foundry. Reprinted with permission Am J Epid 1996; 144: 890–900

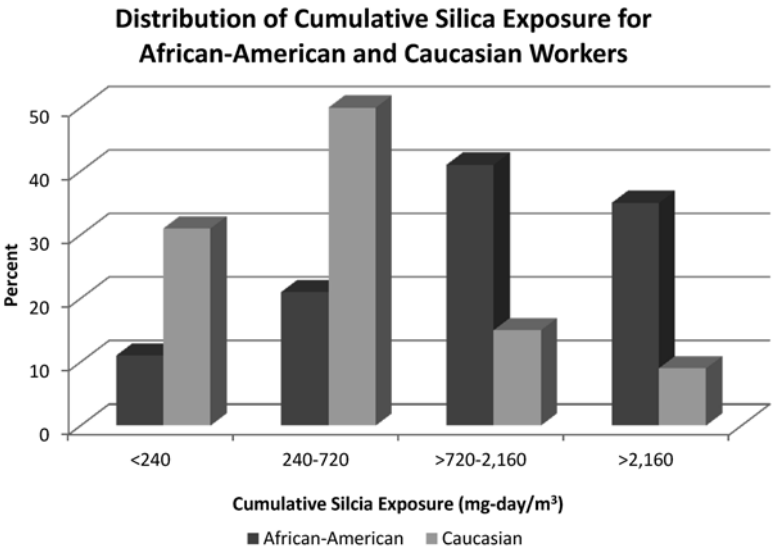

Fig. 4.5 Mean silica exposure for African-American and white workers at a gray iron foundry. Reprinted with permission Am J Epid 1996; 144: 890–900

ling for silica exposure, blacks and whites had a similar prevalence of silicosis [41]. The discriminatory practices leading to placement of black workers in foundries has been well documented [39]. In a collection of interviews conducted by a historian at Michigan State University, retired black foundry workers with confirmed silicosis who had moved from the South for work describe how being black affected job

placement within the foundries [20]. Please see the quote from one of the individuals who were interviewed at the beginning of this chapter.

Example # 3: South African Gold Mines

Occupational health disparity is not unique to the USA. Respiratory exposure disparity has been described among black South African gold miners. The workforce in the South African mines in the 1990s was 600,000, with 90 % of the workers being black. The black workers were the laborers, while white workers were generally in supervisory jobs. The first study of black gold miners was not published until 1991 because black miners were considered transient rural individuals who worked to obtain sufficient money to return to their farms [43]. This first study of black miners was a cross-sectional study that only included current workers, but in spite of that limitation, study investigators found that 857 (71.6 %) of 1197 black miners had silicosis and 62 % had chronic bronchitis including 45 % of the miners who had never smoked cigarettes. In contrast, a study published 13 years earlier of white south African gold miners found that only 134 of 1973 (6.8 %) had silicosis [44]. While the prevalence of chronic bronchitis among the white miners was similar to the results in black miners (62.7 %), the percentage of nonsmokers among black miners was 29.2 % versus 11.3 % among white miners. Although changes since the end of apartheid have ended legislated differences, such as increased compensation rates for white miners who develop silicosis compared to black miners, "race remains an important determinant of occupation, salary, housing and disease burden" [45].

Work-Related Asthma

American Thoracic Society (ATS) consensus statements have determined that 36.5 % of adult asthma is either caused or aggravated by work. The median estimate is that 15 % of adult asthma is caused by work exposures and that 21.5 % of adult asthma is aggravated by work exposures [46, 47].

The prevalence of work-related asthma among adults was calculated from the Behavioral Risk Factor Surveillance System (BRFSS) asthma call-back survey that was administered to a random sample of the general population in 38 states and the District of Columbia from 2006 to 2009 [48]. Work-related asthma was defined as having current asthma and responding yes to the following question: "Were you ever told by a doctor or other health professional that your asthma was related to any job you ever had?" The overall prevalence of work-related asthma was 9.0 % (95 % CI 8.4–9.6). Black and Hispanic participants reported a greater prevalence of work-related asthma compared to white participants (blacks 12.5 % (95 % CI 9.8–15.2), Hispanics 10.5 % (95 % CI 7.7–13.4), whites 8.2 % (95 % CI 7.6–8.8)) [48].

The BRFSS survey did not collect industry or occupation data as a core variable of the survey.

Incidence data from Michigan demonstrated similar differences in work-related asthma by race. The annual incidence rate of work-related asthma for African Americans was 4.8/100,000, which was nearly twofold greater than that of whites (2.5/100,000) [20]. This incidence data was derived from the state's occupational disease reporting system based on reports received from health care facilities and practitioners.

Cross-sectional surveys of the general population have shown marked differences in the prevalence of asthma by occupation [49, 50]. The National Health Interview Survey (NHIS) collects information on industry and occupation as well as self-report of health care provider diagnosed asthma. The overall prevalence of asthma from the combined surveys from 1997 to 2004 was 9.21 % with Blacks having the highest prevalence of 9.42 %, then Whites with a prevalence of 9.28 % and Hispanics with the lowest prevalence of 6.77 %. By occupation, service occupations had the highest prevalence of asthma at 10.58 %, and farming, forestry, and fishing occupations had the lowest prevalence at 6.83 % [50]. Within a given occupation, the prevalence of asthma by race differed from the overall prevalence of asthma by race. For example, among individuals who reported having a service occupation, Whites had the highest prevalence of asthma at 11.01 %, compared with 9.82 % among Blacks and 6.39 % among Hispanics in the same occupation category. Interpretation of this data is limited because the data collected was related to current occupation, which is not necessarily the same occupation that participants had when their asthma began as they may self-select a new occupation after development of their asthma [51]. Additionally, individuals with childhood asthma may self-select into certain occupations [52].

Industries with exposures that cause occupational lung diseases from mineral exposures have typically had a predominately male workforce, i.e., construction and manufacturing, and consequently most cases of pneumoconiosis have occurred in men. An exception to this generalization in gender differences in occupational lung disease is that more cases of work-related asthma are reported in women than men (60 % vs. 40 %) [53]. The more common occurrence of work-related asthma in women can be partially attributed to exposure to allergens in some industries that are predominately female [54] and differential exposure to men and women who are in the same industry, i.e., health care [55].

In addition to considering the work relatedness of asthma, the 2003 ATS statement on occupational airways disease described that work was a significant contributor to the development of COPD in 15 % of cases [46]. Cross-sectional studies of COPD in the general population, like those for asthma, have clearly shown marked differences in prevalence of obstructive lung disease by occupation [50, 56]. While the overall prevalence of COPD is greatest among whites [50, 56], the estimated proportion of cases associated with work is greatest among Mexican Americans (49.6 %), followed by Blacks (23.4 %) and whites 22.2 % [56]. The industries contributing to the attributable fraction of COPD caused by work also differ by race. Among whites, the most important industries were armed forces, rub-

ber, plastics and leather manufacturing utilities, and textile manufacturing. In contrast, among blacks, the related industries included construction, metal and automobile manufacturing, food product manufacturing, and agriculture. Among Mexican Americans, the important industries included agriculture, construction, and services. The authors concluded the higher percentage of COPD attributable to work among Mexican-Americans was due to the lower cigarette smoking burden in Mexican-Americans.

The strongest associations between COPD and specific work-related exposures are with chlorine, coal, cotton dust, silica, and welding fumes [57]. There are no data available that assess current exposure to these substances by age, race, or ethnicity. There are limited data on differential exposures between men and women [54, 55]. It is generally acknowledged that lower socioeconomic, labor intensive jobs are likely to have greater safety and health risks, including exposure to respiratory toxins, than higher socioeconomic white collar/office jobs.

Current Racial Distribution of the US Workforce

This chapter contains multiple historical examples where discrimination in hiring practices led to disparities in the development of occupational respiratory disease. Given the typical long latency between onset of exposure and development of pneumoconiosis or lung cancer, some current racial differences in respiratory disease rates may represent a legacy from past discriminatory hiring practice (i.e., lung cancer). This certainly is the case with the occurrence of silicosis in Michigan. Even though discriminatory hiring practices are now illegal, there are other reasons why there continue to be marked differences in the distribution of the races across occupations. These include residential clustering by race with geographic limitations on the availability of jobs and differences in educational attainment. Table 4.2 shows the distribution of the ten most common occupations where individuals in each race/ethnicity group were employed in Michigan in 2011. The top ten occupations among blacks and Hispanics were service or manual labor; in contrast, six of the ten top occupations of whites and only one among Asians were service or manual labor. The CDC has shown using 2010 data that minorities are overrepresented in occupations having the highest occupational injury rates—24.4 % of Hispanics versus 11.6 % of Blacks versus 3.8 % of Whites are employed in high-risk occupations [2]. This determination of high-risk occupations was based on current work-related injury rates. No similar analysis of the current workforce for occupations with increased risk for respiratory exposures has been performed. Establishment of the Occupational Safety and Health Administration in 1970 and the implementation of workplace standards and reductions in exposures for respiratory toxins over time have ideally made the workplace safer for all workers. However, there continues to be documentation of disparities in work-related injuries [4–7]. On the other hand, there have been no dramatic disparities in mortality from work-related lung cancer documented

Table 4.2 Ten most common occupations for Hispanics, African Americans, Asians and Whites, Michigan 2011[a]

Hispanic (# *employed*: *161,489*)	*African Americans* (#*employed*: *435,105*)
Agricultural workers (9.8 %)	Nursing/home health aides (4.6 %)
Assemblers and fabricators (4.1 %)	Janitors (3.1 %)
Grounds maintenance workers (3.1 %)	Assemblers and fabricators (3.1 %)
Retail salespersons (3 %)	Personal and home care aides (2.8 %)
Janitors (2.8 %)	Cashiers (2.8 %)
Cooks (2.5 %)	Laborers (2.5 %)
Food preparation workers (2.2 %)	Customers service reps (2.4 %)
Packers and packagers, hand (2.2 %)	Retail salespersons (2.3 %)
Waiters/waitresses (1.9 %)	Cooks (2.2 %)
Secretaries (1.8 %)	Bus drivers (2.1 %)
Asian (# *employed*: *129,414*)	*White* (# *employed*: *white—3,558,662*)
Mechanical engineers (9 %)	Cashiers (2.4 %)
Software developers (7.5 %)	Retail salesperson (2.4 %)
Postsecondary teachers (4.3)	Driver/sales workers and truck drivers (2.8 %)
Computer/information systems managers (3.9 %)	Secretaries (2.3 %)
Physical therapists (3.9 %)	Managers, all other (2.1 %)
Managers (3.4 %)	Nurses (2.1 %)
Nurses (3.1 %)	Elementary/middle school teachers (2.1 %)
Cooks (2.9 %)	Supervisors of retail sales workers (1.9 %)
Accountants (2.9 %)	Waiters/waitresses (1.6 %)
Physicians (2.7 %)	Assemblers/fabricators (1.5 %)

[a]Rankings of most common occupations are from the 2011 Current Population Survey, U.S. Bureau of Census. Occupations are the occupational categories used by the Bureau of Census [http://www.census.gov/people/io/methodology]
Percents in the table are the percent of all employed members of that race/ethnicity group who work in that particular occupation (Table adapted from ref [20]

in the medical literature for the last 30 years. The overrepresentation of minorities in certain occupations such as service occupations (see Table 4.2) indicates the potential for ongoing occupational respiratory disparities secondary to differential exposure risks. For example, service workers have an increased prevalence of asthma [50] and are likely to have an increased potential for exposure to cleaning agents, which are associated with the development of work-related asthma [58].

Given the documented deficiencies in the current occupational surveillance system, changes are necessary if we are to accurately assess the occurrence of current and future occupational respiratory health disparities. The modifications needed include adding race to surveillance systems that already collect information on work-related injuries and illnesses and adding information on occupation and industry to surveys/medical records that collect medical and race data. Recommendations include: (1) requiring the reporting of race in the annual Bureau of Labor Statistics employer-based survey on injuries and illnesses; (2) adding race as a core variable

in worker compensation state data systems; (3) adding industry and occupation to the core module of the annual BRFSS survey administered in the 50 states; and (4) routinely collecting information about occupation/employer in medical records and making collection of such information a requirement for future meaningful use incentives as part of the transition to electronic medical health records [59]. Successful implementation of the above changes will not only allow for the generation of valuable data on occupational respiratory health disparities but will also allow for development of targeted interventions.

Acknowledgements Grant sponsor: National Institute for Occupational Safety and Health. Grant # U60 OH008466.

References

1. Centers for Disease Control and Prevention Office of Minority Health & Health Equity. http://www.cdc.gov/minorityhealth/OMHHE.html. Accessed 7 July 2014.
2. Centers for Disease Control and Prevention. Health disparities and inequalities report—United States. MMWR. 2013;62 Suppl 3:1–187.
3. Berman D. Death on the Job: occupational health and safety struggles in the United States. New York: Monthly Review Press; 1978. p. 9.
4. Robinson JC. Exposure to occupational hazards among Hispanics, blacks and non-Hispanic whites in California. Am J Public Health. 1989;79:629–30.
5. Simpson CL, Severson RK. Risk of injury in African American hospital workers. J Occup Environ Med. 2000;42:1035–40.
6. Cierpich H, Styles L, Harrison R, Davis L, Chester D, Lefkowitz D, Valiante D, Richardson S, Castillo D, Romano N, Baron S. Work-related injury deaths among Hispanics—United States, 1993–2006. Morb Mortal Wkly Rep. 2008;57:597–600.
7. Byler CG. Hispanic/Latino fatal occupational injury rates. Mon Labor Rev. 2013;136(2):14–23.
8. Leigh PJ. 2012. Numbers and costs of occupational injury and illness in low-wage occupations. Center for Poverty Research and Center for Health Care Policy and Research, University of California Davis. http://defendingscience.org/sites/default/files/Leigh_Low-wage_Workforce.pdf. Accessed 7 July 2014.
9. U.S. Public Health Service. Health of workers in chromate producing industry. Washington DC Public Health Service 1953; Publication No. 192. 1–131.
10. Lloyd WF. Long-term mortality study of steel workers: V. Respiratory cancer in coke plant workers. J Occup Med. 1971;13:53–68.
11. McMichael AJ, Spirtas R, Gamble JF, Tousey PM. Mortality among rubber workers: relationship of specific jobs. J Occup Med. 1976;18:178–85.
12. Martin CF, Higgins JE. Byssinosis and other respiratory ailments: a survey of 6,631 cotton textile employees. J Occup Med. 1976;18:178–85.
13. Cherniak M. The Hawk's nest incident. America's worst industrial disaster. New Haven: Yale University Press; 1986. p. 194.
14. Roscoe RJ, Deddens JA, Salvan A, Schnorr TM. Mortality among Navajo uranium miners. Am J Public Health. 1995;85:535–40.
15. Murray LR. Sick and tired of being sick and tired: scientific evidence, methods, and research implications for racial and ethnic disparities in occupational health. Am J Public Health. 2003;93:221–6.
16. Lipscomb H, Loomis D, McDonald MA, Argue RA, Wing S. A conceptual model of work and health disparities in the United States. Int J Health Serv. 2006;26:25–50.

17. National Institute for Occupational Safety and Health. 2012a. Occupational health disparities program description. http://www.cdc.gov/niosh/programs/ohd/ Accessed 7 July 2014.
18. Souza K, Steege AL, Baron SL. Surveillance of occupational health disparities: challenges and opportunities. Am J Ind Med. 2010;53:84–94.
19. Bureau of Labor Statistics. 2012. News release: non-fatal injuries and illnesses requiring days away from work: 2011. http://www.bls.gov/iif/ Accessed 7 July 2014.
20. Stanbury M, Rosenman KD. Occupational health disparities: a state public health-based approach. Am J Ind Med. 2014;57:596–604.
21. Rosenman KD, Stanbury MJ. Risk of lung cancer among former chromium smelter workers. Am J Ind Med. 1996;29:491–500.
22. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 92. Lyon: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; 2005. p. 1–868.
23. Lloyd JW, Lundin FE, Redmond CK, Geiser PB. Long-term mortality study of steelworkers. IV. Mortality by work area. J Occup Med. 1970;12:151–7.
24. Redmond CK, Ciocco A, Lloyd JW, Rush HW. Long-term mortality study of steelworkers. VI. Mortality from malignant neoplasms among coke oven workers. J Occup Med. 1972;14:621–9.
25. Costantino JP, Redmond CK, Bearden A. Occupationally related cancer risk among coke oven workers: 30 years of follow-up. J Occup Environ Med. 1995;37:597–604.
26. Mazumdar S, Redmond C, Sollecito W, Sussman N. An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. J Air Pollut Control Assoc. 1975;25:382–9.
27. Moolgavkar SH, Luebeck EG, Anderson EL. Estimation of unit risk for coke oven emissions. Risk Anal. 1998;18:813–25.
28. Redmond CK. Cancer mortality among coke oven workers. Environ Health Perspect. 1983;52:67–73.
29. Michaels D. Minority workers and occupational cancer: the hidden costs of job discrimination in behavior, health risks and social disadvantage. Summary of a Conference. In: Parron DL, Solomon F, Jenkins CD, editors. Washington DC: National Academy Press 1982, contract # 282-78-0163-EJM: pp. 43–50.
30. Goldsmith JR. Geographical pathology as a method for detecting occupational cancer. J Occup Med. 1977;19:533–9.
31. Brugge D, Goble R. The history of uranium mining and the Navajo people. Am J Public Health. 2002;92:1410–9.
32. Gilliland FD, Hunt WC, Pardilla M, Key CR. Uranium mining and lung cancer among Navajo men in New Mexico and Arizona, 1969–1993. J Occup Environ Med. 2000;42:278–82.
33. Mulloy KB, James DS, Mohs K, Kornfeld M. Lung cancer in a nonsmoking underground uranium miner. Environ Health Perspect. 2001;109:305–9.
34. Samet JM, Kurtvirt DM, Waxweiler RJ, Key CR. Uranium mining and lung cancer in Navajo men. N Engl J Med. 1984;310:1481–4.
35. Roscoe RJ. An update of mortality from all causes among white uranium miners from the Colorado Plateau Study Group. Am J Ind Med. 1997;31:211–22.
36. Hornung RW, Meinhardt TJ. Quantitative risk assessment of lung cancer in U.S. uranium miners. Health Phys. 1987;52:417–30.
37. Mapel DW, Coultas DB, James DS, Hunt WC, Stridley CA, Gilliland FD. Ethnic differences in the prevalence of nonmalignant respiratory disease among uranium miners. Am J Public Health. 1997;87:833–8.
38. NIOSH Hazard Review. Health effects of occupational exposure to respirable crystalline silica. DHHS (NIOSH) Publication No. 2002–129. http://www.cdc.gov/niosh/docs/2002-129/pdfs/2002-129.pdf Accessed 7 July 2014.
39. Foote CL, Whatley WC, Wright G. Arbitraging a discriminatory labor market; Black workers at the Ford Motor Company, 1918–1947. J Labour Econ. 2003;21:493–532.

40. Rosenman KD, Reilly MJ, Kalinowski D. 2010 annual report on silicosis in Michigan. E. Lansing Michigan. 2012. http://www.oem.msu.edu/userfiles/file/Annual%20Reports/Silica/2010SilicosisAnnualReport.pdf. Accessed 7 July 2014.
41. Rosenman KD, Reilly MJ, Rice C, Hertzberg V, Tseng CY, Anderson HA. Silicosis among foundry workers: implications for the need to revise the OSHA standard. Am J Epidemiol. 1996;144:890–900.
42. Rice C, Rosenman KD, Reilly MJ, Hertzberg VS. Reconstruction of silica exposure at a foundry for evaluation of exposure-response. Ann Occup Hyg. 2002;46 suppl 1:10–3.
43. Cowie RL, Mabena SK. Silicosis, chronic airflow limitation and chronic bronchitis in South African gold miners. Am Rev Respir Dis. 1991;143:80–4.
44. Irwig LM, Rocks P. Lung function and respiratory symptoms in silicotic and nonsilicotic gold miners. Am Rev Respir Dis. 1978;117:429–35.
45. Murray J, Davies T, Rees D. Occupational lung disease in the South African mining industry: research and policy implementation. Am J Public Health. 2011;32:S65–79.
46. Balmes J, Becklake M, Blanc P, et al. American thoracic society statement: occupational contribution to the burden of airway disease. Am J Respir Crit Care Med. 2003;167:787–97.
47. Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemiére C, Martin J, Tarlo SM, Vandenplas O, Torén K. An official American thoracic society statement: work-exacerbated asthma. Am J Resp Crit Care Med. 2011;184:368–78.
48. Centers for Disease Control and Prevention. Work-related asthma—38 states and District of Columbia, 2006–2009. Morb Mortal Wkly Rep. 2012;61:375–8.
49. Bang KM, Hnizdo E, Doney B. Prevalence of asthma by industry in the US population: a study of 2001 NHIS data. Am J Ind Med. 2005;47:500–8.
50. Fleming LE, Pitman T, LeBlanc W, Lee D, Bridges KC, Martinez AC, Christ S, McCollister K, Arheart K, Ferraro K. Occupations and health disparities: the national health interview survey 1997–2004. Department of Epidemiology and Public Health, University of Miami School of Medicine March 2007. http://www.umiamiorg.com/publications/monograph/health_disparities.html. Accessed 7 July 2014.
51. Knoeller GE, Mazurek JM, Storey E. Occupation held at the time of asthma symptom development. Am J Ind Med. 2013;56:1165–73.
52. Mazurek JM, Schleiff PL, Henneberger PK. Is childhood asthma associated with educational level and longest-held occupation? Am J Epidemiol. 2012;175:279–88.
53. White GE, Seaman C, Filios MS, Mazurek JM, Flattery J, Harrison RJ, Reilly MJ, Rosenman KD, Lumia ME, Stephens AC, Pechter E, Fitzsimmons K, Davis LK. Gender differences in work-related asthma: surveillance data from California, Massachusetts, Michigan, and New Jersey, 1993–2008. J Asthma. 2014;51(7):691–702.
54. Gautrin D, Cartier A, Howse D, Horth-Susin L, Jong M, Swanson M, Lehrer S, Fox G, Neis B. Occupational asthma and allergy in snow crab processing in Newfoundland and Labrador. Occup Environ Med. 2010;67:17–23.
55. Dumas O, Donnay C, Heederik DJ, Hery M, Choudat D, Kauffmann F, LeMoual N. Occupational exposure to cleaning products and asthma in hospital workers. Occup Environ Med. 2012;69:883–9.
56. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Airflow obstruction attributable to work in industry and occupation among U.S. race/ethnic groups: a study of NHANES III data. Am J Ind Med. 2004;46:1126–35.
57. Balmes JR. Occupational contribution to the burden of chronic obstructive pulmonary disease. J Occup Environ Med. 2005;47:154–60.
58. Rosenman KD. Cleaning products-related asthma. Clin Pulm Med. 2006;13:221–8.
59. Institute of Medicine. 2011. Incorporating occupational information in electronic health records: letter report. Washington DC: The National Academies Press. http://www.nap.edu/catalog.php?record_id=13207. Accessed 7 July 2014

Chapter 5
Health Disparities and Pulmonary Function Testing

Joseph H. Skalski, Rachele A. Gibson, Sarah A. Narotzky, Hemang Yadav, and Paul D. Scanlon

Key Points

- Pulmonary function tests (PFTs) are necessary for the accurate diagnosis and management of most lung diseases. They are underutilized in nearly all patient populations, but particularly in the underprivileged who face many barriers to receiving high-quality care including undergoing PFTs.
- Unlike some medical tests, PFTs are highly performance dependent, meaning that patients must understand and follow complex instructions to achieve accurate results. Language and cultural barriers between testing personnel and patients can lead to inaccurate PFTs.
- Pulmonary function tests are interpreted in comparison with predicted normal values derived from large cohorts of healthy individuals.
- Differences in lung function have been observed by self-identified race. Race is therefore used as a corrector for the calculation of predicted normal values.
- Environmental and socioeconomic factors can affect pulmonary function. This likely explains some but not all of the observed differences in lung function by race.
- The use of "race correction" to calculate predicted normal values has generated controversy, but it likely results in more accurate estimation of lung function. Each individual patient's results must be interpreted in their clinical context.

J.H. Skalski, M.D. • R.A. Gibson, M.D. • S.A. Narotzky, M.D. • H. Yadav, M.B.B.S. • P.D. Scanlon, M.D. (✉)
Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA
e-mail: pscanlon@mayo.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_5

Overview of Pulmonary Function Testing

The primary function of the lungs is the exchange of gases between the environment and the blood stream. This function can be measured as a series of flows and volumes inhaled and exhaled during breathing maneuvers and by measures of gas exchange into the blood stream. Pulmonary function tests (PFTs) include a variety of diagnostic procedures used to identify and quantify abnormalities in lung function. Among the most widely used PFTs are spirometry, measurement of lung volumes, and measurement of diffusing capacity. Spirometry is measurement of forced air flow and volume over time after a maximal inhalation. Multiple variables are measured and reported, including the maximum volume exhaled in the first second (FEV_1) and the total volume of air exhaled after a single maximal inhalation, the forced vital capacity (FVC). Spirometry can be performed with a simple handheld device. Lung volume testing measures the total volume of air in the lungs ranging from total lung capacity (TLC) at full inspiration down to the air remaining in the lungs after full exhalation, the residual volume (RV). Measurement of lung volumes requires more complex equipment such as a plethysmography chamber, commonly known as a body box. Diffusing capacity is a test in which the lungs' ability to absorb carbon monoxide gas is measured as a surrogate of their ability to absorb oxygen and eliminate carbon dioxide. When these results are put together, PFTs can classify abnormal lung function into either an obstructive or restrictive pattern with or without an associated gas transfer abnormality, and each pattern is associated with different diseases of the lung.

An important aspect of lung function testing is that accurate testing is highly dependent on patient performance. This is different from many other medical tests, such as vital sign measurements or blood tests, which do not necessarily require patients to understand and follow complex instructions in order to achieve accurate results. For example, to obtain reliable results during spirometry, the patient must take in a maximal breath and then make a maximal rapid and forceful effort of exhalation. A deviation from this procedure will usually result in underestimation of the FEV_1 and FVC. A well-trained technician is essential for accurate PFT performance. The technician provides coaching to each patient to ensure maximal performance during the spirometry test. Technicians must be able to review spirometry curves, recognize common performance errors, reinstruct the patient, and repeat the test as needed to achieve maximal results. Without appropriate instruction and coaching, patients may have suboptimal effort resulting in unreliable results. In particular, submaximal spirometry performance may result in overestimating the severity of lung disease or even result in the diagnosis of lung disease where there is none. This is true of most other modalities of PFTs as well. All of this makes PFTs more sensitive than many other medical diagnostic tests to linguistic and cultural barriers that may exist between testing personnel and the patient. Furthermore, for a patient to have access to accurate PFTs, they must not only have access to a medical facility with equipment and willingness to perform the PFTs, but they must also have appropriately trained technicians at that facility, assisted by translators when necessary, to perform maximal and error-free tests.

Health Disparities and Performance of PFTs

Access to Pulmonary Function Testing

PFTs are typically used for the diagnosis and monitoring of lung diseases, most commonly obstructive lung disease (e.g., asthma and COPD). However, patients do not present with defined diseases, but rather with undifferentiated symptoms such as dyspnea, cough, and wheezing. To prevent misdiagnosis and thus misdirected medical care, current COPD and asthma guidelines unanimously require the use of PFTs for disease diagnosis, assessment of disease severity, and ongoing disease monitoring [1, 2]. The National Committee for Quality Assurance (NCQA) has adopted spirometry as a performance measure in patients with a new diagnosis of COPD.

Despite these recommendations and the high social and economic burden of these diseases, utilization of spirometry remains low. COPD itself is underdiagnosed in the general U.S. population. Figure 5.1 shows data from the Third National Health and Nutrition Examination Survey (NHANES III), a survey of the general U.S. population that included health questions and medical tests including spirometry. As illustrated in the figure, many participants were found to have obstructive airflow limitation on spirometry, including severe limitation, even if they had never previously been diagnosed with COPD. These individuals were not asymptomatic and instead reported substantial burden of respiratory limitations on the health survey [3], suggesting that they would likely benefit from diagnosis and treatment of their lung disease.

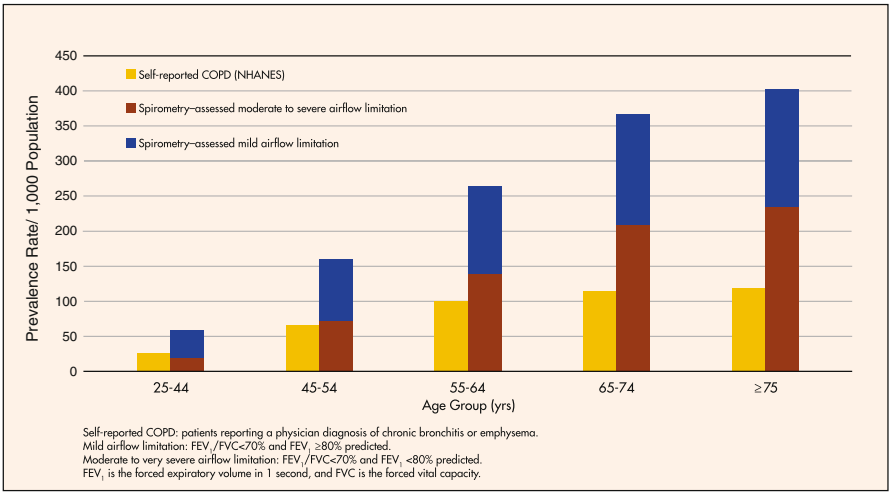

Fig. 5.1 Underdiagnosis of COPD in the absence of routine spirometry. Reproduced with permission from *Insights for Improvement*: *Advancing COPD Care Through Quality Measurement*. Copyright © 2009 by the National Committee for Quality Assurance (NCQA). To access a copy of this publication, visit http://www.ncqa.org

Even among patients who do receive a diagnosis of COPD, spirometry is underutilized. In a 2007 review of over 5000 patients newly diagnosed with COPD, just 32 % had any PFTs prior to disease diagnosis [4]. Similarly, a review of around 200,000 Veteran Affairs patients newly diagnosed with COPD found the frequency of spirometry testing was around 34 % [5]. Both studies found the frequency of spirometry testing lower among older patients. Additionally, several studies have established that the burden of asthma and respiratory disease is not uniform across all patient groups. Ethnic minorities and those with lower socioeconomic status (SES) have increased morbidity and mortality related to asthma, with lack of access to healthcare, including PFTs, implicated [6–13].

The lack of routine PFTs in these settings has a number of potential consequences for patient care. Limited use of PFTs in the initial evaluation of patients with possible COPD has been shown to increase the risk of underdiagnosis of COPD. Confirmation of the diagnosis of asthma/COPD with PFTs results in better overall care, giving providers greater confidence in prescribing medications appropriately for moderate to severe COPD, such as anticholinergic inhaler therapy and long-acting beta agonists [14]. Additionally, there is a risk of misdiagnosis or "overdiagnosis," with patients being exposed to treatments for conditions they don't have, as well as delayed or missed diagnosis of other serious disorders. Misdiagnosis can also lead to patients being "labeled" with chronic medical conditions, with resulting psychosocial stigmata, as well as increased premiums for health and life insurance. When COPD or asthma is misdiagnosed, often due to lack of spirometry, prescription of inhaled bronchodilator medications can be ineffective and wasteful. This is particularly true when patients experience an apparent response to therapy because of spontaneous resolution of self-limited conditions such as viral respiratory tract infections. This can result in undesirable medication side effects, as well as financial burden from having to purchase inhalers or nebulizers. Many inhalers have a monthly cost of $100–$300, so this financial burden may be considerable.

Many factors may contribute to underutilization of spirometry in primary care settings, but exact reasons for underutilization have not been adequately explored. Many laboratories have substantial wait times prior to pulmonary function testing being available. Long waiting times (as long as several weeks) may be a sufficient disincentive to prevent some otherwise appropriate testing. In our pulmonary function laboratory, we operate with the assumption that "unmet demand goes away" and manage test availability with a targeted maximum wait time of 2 days and immediate accommodation of patients who show up requesting immediate testing.

Perhaps the greatest contributing factor to lack of test availability is lack of the most expensive component of the testing system: well-trained staff who can coach patients to perform acceptable and repeatable PFTs. Comprehensive technician training and a program of quality assurance and feedback have been shown to improve the quality of spirometry results [15]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have published standardization guidelines for spirometry [16, 17]. In surveys of general practitioners, lack of confidence in the quality of the spirometry measure was felt to be a major limitation to widespread utilization of PFTs in primary care practice [18]. Prior studies noted that

spirometry performed in family practice settings without technician training frequently does not satisfy ATS/ERS criteria for acceptability and repeatability. However, following relatively simple training, the proportion of maneuvers achieving quality standards increased substantially, highlighting the importance of effective training and quality assurance programs to ensure successful spirometry in primary care practice [19]. Crucially, several studies have demonstrated that when spirometry is performed in primary care practices by healthcare professionals trained to appropriately coach patients through spirometry maneuvers, the quality of spirometry results was comparable to those performed in a specialist-run pulmonary function laboratory [20].

As noted earlier, the utilization of PFTs in newly diagnosed COPD cases is lower among older patients [4, 5]. Part of this age discrepancy may be out of concern for poor test quality in older adults. In the SARA study, spirometry reproducibility and acceptability was assessed for older adults (>65 years) undergoing PFTs for the diagnosis of asthma or COPD. Investigators found that testing in older adults typically required more time and more attempts. However, if this was done with rigorous quality control measures implemented, good spirometry test quality was achievable with result quality comparable to that among younger patients. Cognitive impairment, a shorter 6-min walk distance, and lower educational level were all found to be independent predictors for a poorer acceptability rate [21].

Spirometry certification programs exist both nationally and internationally to provide the necessary training. In the United States, certification was established through the Cotton Dust Standard [29 CFR 1910.1043] and is coordinated by the National Institute for Occupational Safety and Health (NIOSH). Initial certification requires 15 h of training. A 1-day recertification program is required every 5 years. In addition to time and money, another potential roadblock to certification is not having geographical proximity to one of the NIOSH-approved training centers [22]. In primary care clinics where adequate technician training limits the availability of quality PFTs, a possible alternative is spirometry performed locally within the clinic, but coordinated and coached online by certified technicians working at a separate pulmonary function laboratory. This concept has been shown to provide an adequate alternative to conventional spirometry in primary care centers [23]. Once staff members have been appropriately trained to perform spirometry or other tests, ongoing staff management is required to provide test availability when needed. In the primary care setting, this includes juggling of other duties for busy staff who may be nurses, respiratory therapists, phlebotomists, or other laboratory or clinical personnel. Most have other tasks that must be prioritized.

Equipment availability, by contrast, is probably rarely a legitimate limitation to availability of PFTs in the United States and other developed countries. Although pulmonary function equipment capable of complete PFTs (including lung volumes and diffusing capacity in addition to spirometry) typically cost more than $30,000, a simple office spirometer can be purchased for under $1000, and a more comprehensive spirometry system can be purchased for less than $5000 complete with computer and printer. Medicare reimbursement for spirometry with bronchodilator is over $70 per test, though Medicaid reimbursement is less. The test requires

20–30 min of staff time and the only disposable cost is for a filter/mouthpiece, which typically costs $1–5. Reimbursement for healthcare services in the United States typically underpays for cognitive services but overpays for procedural services, so the underutilization of spirometry seems curious and illogical. As stated earlier, we believe lack of timely test availability is a major unrecognized contributing factor.

As discussed elsewhere in this text, asthma has increased disease prevalence among low-income and inner-city communities, those with lower educational attainment (high school or less), women, and African-Americans [13]. Over time, there has been a widening of the racial differences in asthma severity, with studies suggesting African-Americans may be more likely to have asthma hospitalizations, greater severity of disease, and higher asthma-related mortality [8, 10–12]. Cigarette smoking remains a major modifiable risk factor for developing respiratory diseases, and the burden of cigarette smoking is similarly disproportionate—greater in those living below the poverty level, with lower educational levels, and within certain ethnicities (particularly Native Americans) [24, 25]. The prevalence of cigarette smoking has declined over time, thanks to concerted public health campaigns, increased taxation on cigarettes, prohibition of indoor cigarette smoking, antitobacco mass media campaigns, and barrier-free access to smoking cessation aids [24]. These public health efforts need to continue and should be focused on communities and groups in which prevalence of cigarette smoking remains high. Inner-city communities also have increased exposures to airborne particulate matter and other vehicle emissions [26, 27]. These exposures have been linked to declines in lung function in the general population [27, 28], which are likely even greater for the elderly and patients with chronic respiratory conditions [29]. Other potentially significant exposures seen more commonly among inner-city residents include inhaled drugs such as crack cocaine and greater exposure to certain antigens such as from cockroaches and dogs [30–32].

Inner-city and poorer communities also have lower doctor-to-patient ratios, resulting in less time per clinic visit, less continuity of care, greater proportion of care in emergency room and urgent care settings, as well as longer waiting times for routine appointments [33, 34]. Quality of asthma care has been shown to be lower for inner-city patients with asthma, particularly within ethnic minorities and those living in poorer neighborhoods [6, 7, 9, 12]. In these time-pressured settings, often in urgent care centers without established patient–provider relationships, diagnostic accuracy including evaluation with spirometry may be neglected in favor of "quick fixes" such as empiric antibiotics, rescue inhalers, and oral corticosteroids. Patients may have lower rates of insurance coverage and indicated diagnostic testing such as spirometry may be skipped because of patients' inability to pay [34].

Another barrier to access may be lack of transportation. In the inner-city setting, testing facilities are likely to be close—within a few miles of a patient. However, in the absence of affordable, accessible, and safe mass transit systems, getting to clinics may be time or cost prohibitive. In the rural setting, including Native American reservations, the opposite problem exists, where distances may be great. Consequently, patients require not only vehicles, but also money for gasoline and

the ability to take time off from work. Again, this can be time and cost-prohibitive. The ultimate result is less access to PFTs, and a greater proportion of patients with underdiagnosed, misdiagnosed, or mismanaged pulmonary conditions, including not only asthma and COPD, but also other less common conditions which are frequently misdiagnosed as asthma or COPD until more thoughtful evaluation is pursued.

Language barriers and Pulmonary Function Testing

Patients with limited English proficiency face additional barriers to accessing high-quality PFTs in the United States. It has been well established that ensuring adequate communication in the healthcare setting is critical in providing safe and efficacious care for those with limited English proficiency [35]. Language barriers in the United States and around the globe can lead to suboptimal healthcare delivery and poor health outcomes [36]. Federal requirements in the United States related to culturally and linguistically appropriate services have been crucial in helping to change how medical interpretation is viewed. The Office of Minority Health developed "National Standards on Culturally and Linguistically Appropriate Services" to help hospitals ensure quality care for diverse patient populations [37]. Despite these standards, clinics and hospitals often still utilize family members and friends to serve as interpreters. Additionally, the use of interpreters accessible by telephone or other communications media has risen drastically, especially in areas with limited availability of in-person services. While telephone interpreters provide a much needed service, they lack the ability to provide the nuances of face-to-face interactions that can be critical in many medical interactions.

The diversity of the United States population continues to increase. According to data collected from NHANES from 1999 to 2004, nearly 16 % of the sampled individuals spoke a language other than English, which was most commonly Spanish (96 %, though Mexican-Americans were oversampled) with the remaining individuals (4 %) speaking 30 different languages. Language interpreters must work "on the spot" and convey spoken words from one language to another. A common misconception is that individuals (including clinic staff and patient families) that are bilingual can serve as interpreters with no difficulty; however, those with no formal training are more likely to add or omit information in an exchange between examiner and patient. In addition, individuals who are unfamiliar with using language interpreters often do not speak directly to the patient, which can alienate that individual. They also tend to speak in long sentences, can unintentionally patronize or infantilize adults with limited English abilities, and often raise their voice, although the patient is not hearing impaired [38].

Language barriers are not insurmountable. At Mayo Clinic Rochester, interpretation services for 17 languages are provided by in-person interpreters available daily, including American Sign Language, Arabic, Bosnian/Croatian/Serbian, Cambodian, Chinese Mandarin, Dinka, French, Italian, Lao, Somali, Spanish, Swahili,

Taiwanese, and Vietnamese. With advanced notice interpretation services are available for Greek, Hebrew, Japanese, Korean, and Russian speakers. A "Language Line" telephone interpreter service is available for many additional languages and dialects. Olmsted County, in which Mayo Clinic Rochester is located, is one of the fastest growing counties in Minnesota, with Rochester being the fastest growing metropolitan area in the state. According to the 2006 Census, the resident population of Olmsted County is 137,521, with 70 % of the population living in Rochester. Minorities (races other than White or Hispanic-Latino ethnicity) make up 11 % of the county's population [39]. Enrollment in the Rochester Public Schools shows that 20.9 % of students are classified as minority. Diversity is further reflected in the fact that K-12 students speak more than 53 languages in their homes [39]. Despite the vast resources available at such tertiary medical centers to provide interpreters during patient visits and other testing, there remain instances when family and friends are relied upon to provide interpretation. Sadly, not all medical centers have such resources, and at times there is no access to even basic translation services.

The importance of language and communication is evident in PFTs, where the technician must work closely with the patient to ensure proper technique. The importance of the use of medical translators in the pulmonary function lab is exemplified by a 31-year-old Somali-speaking woman who was referred to Mayo Clinic for further evaluation of abnormal PFTs. The outside pulmonary testing was performed for nonspecific cough, tightness in throat, and episodic shortness of breath following an upper respiratory tract infection (URI). There was no evidence of wheezing or other pulmonary abnormality on physical exam, with the only pertinent physical finding being morbid obesity.

Spirometry performed without an interpreter at an external site is shown in the left panel of Fig. 5.2, demonstrating evidence of severe obstruction (FEV_1 0.89 L, 31 % predicted; FVC 2.10 L, 62 % predicted; FEV_1/FVC 42.4 %). She was also reported to have a severe reduction in DLCO (8.0 mL/min/mmHg, 30 % predicted) and a small improvement after bronchodilator. The outside provider ordered a CT scan of the chest, which was negative, and referred the patient for pulmonary, otolaryngology (ENT), and gastroenterology consultations. Repeat spirometry, performed with a Somali interpreter, is shown in the right panel of Fig. 5.2. The repeat test shows borderline restriction, likely secondary to obesity, with no evidence of airflow obstruction (FEV_1 2.27 L, 79 % predicted; FVC 2.55 L, 75 % predicted; FEV_1/FVC 89.0 %) or bronchodilator response and normal DLCO (24.2 mL/min/mmHg, 99 % predicted). This example demonstrates how the services of an interpreter drastically improved the patient's ability to perform PFTs. Without the additional data provided by the second round of pulmonary testing, the patient might have undergone additional unnecessary testing, and she might have been erroneously labeled with severe lung disease and treated with expensive and potentially harmful medications. The use of interpreters for PFTs for non-native-English speakers has not been directly studied; however, experience shows that coaching a patient in their native language provides the best results.

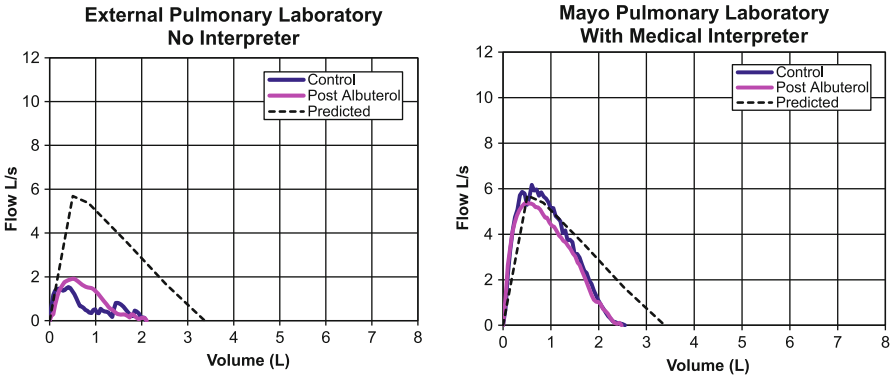

Fig. 5.2 Comparison of spirometry performed with and without a medical interpreter. *Left panel* shows spirometry performed with no interpreter. Severe obstruction is noted with a severe reduction in DLCO. Some improvement with bronchodilator noted. *Right panel* shows near normalization of the spirometry curve when testing is repeated with assistance of a Somali interpreter (patient's native language) to coach the patient through the maneuvers

Description of Respiratory Symptoms: Cultural Variations among English Speakers

Even among English speakers, cultural variations in language utilization and word selection can create communication barriers. Caucasians and African-Americans may select different words to describe the symptom of dyspnea [40]. Healthcare providers may fail to recognize that their patient's symptoms are due to respiratory disease resulting in underutilization of PFTs. In a study of African-Americans with asthma in Nashville, Tennessee, participants were broken into focus groups where they discussed their perception of asthma symptoms and severity. Common symptom descriptions included *breathing problems*, *chest tightness* or *pain*, *wheezing*, *sweating*, and *dizziness*. Overall, it was found that the study participants denied feeling that they were unable to "get air in" [41]. In a follow-up study, both African-American and Caucasian study participants were asked to complete a questionnaire reporting asthma symptoms, and it was found that African-Americans use descriptive terms to report their symptoms that differ from Caucasians [42]. Nocturnal awakenings, dyspnea, chest pain, throat pain, and fatigue were all descriptors used to report asthma symptoms that were used more frequently by Caucasians than African-Americans [42].

In another study, differences between word descriptors of dyspnea were assessed among four different groups, including African-Americans, Hispanic-Americans, Asian-Pacific Islanders, and Caucasians [40]. Caucasian subjects used primarily lower airway ethnic word descriptors (EWDs), such as *chest heavy*, *wheezing*, *deep breathing*, *out of air*, and *hurts to breathe*. There were several distinct upper airway

descriptors used by Asian-Pacific Islanders and African-Americans, including *itchy throat*, *itchy*, *itchy at back of throat*, *tight throat*, and *cough*. Hispanic-Americans used both upper and lower airway word descriptors to describe their symptoms. This study showed different ethnic groups used different terms to describe the same disease process and symptoms. The use of upper airway terminology goes against what most healthcare providers have been taught to associate with breathlessness [40]. This indicates that minority patients may use words to describe an acute asthma flare that some healthcare providers do not associate with the disease.

Health Disparities and Interpretation of PFTs

Reference Values in Pulmonary Function Testing

An important component of interpretation of PFTs is comparing the measured result to a reference standard or predicted value. This is usually reported as a "percent predicted" for each measurement. Reference values vary with sex, age, height, and ethnicity. For example, a healthy 60-year-old white woman who is 165 cm (5′5″) tall is expected to have an FEV_1 value of 2.65 L whereas a healthy 25-year-old white man who is 188 cm (6′2″) is expected to have an FEV_1 value of 5.10 L [43]. PFT reports include the value of each lung measurement as well as the predicted normal value and the percent of the predicted value. If the 60-year-old woman had a measured FEV_1 of 2.12 L, she would be reported to have FEV_1 of 80 % percent predicted.

The "percent-predicted" value is used to diagnose disease or quantify the severity of disease. For example, the widely used GOLD criteria (Table 5.1) for chronic obstructive pulmonary disease (COPD) categorize the severity of COPD based on the percent-predicted value for the postbronchodilator FEV_1 [44]. Patients with different degrees of severity are often prescribed different medications or therapies.

Accurate reference values are extremely important when using PFTs to diagnose disease. Flawed calculation of reference values can lead to underdiagnosis or overdiagnosis of disease. Numerous reference equations have been developed to calculate normal values. The ATS and ERS lung function testing guidelines published in 2005 list over three dozen published spirometry reference equations from around the world [45]. These reference equations are generally derived from large groups of healthy nonsmoking individuals with presumed normal lung function who have

Table 5.1 GOLD staging for severity of COPD [44]

Stage	FEV1 (%)	Severity
I	>80	Mild
II	50–79	Moderate
III	30–49	Severe
IV	<30	Very severe

AGE DISTRIBUTION OF THE SELECTED REFERENCE POPULATION

	Age (*yr*)												
	8–13		14–20		21–35		36–50		51–65		66–80		Total
	n	%	n	%	n	%	n	%	n	%	n	%	(*n*)
Male subjects													
Caucasian	268	30	154	17	192	21	124	14	70	8	90	10	898
African-American	351	34	254	25	251	24	109	11	35	3	27	3	1,027
Mexican-American	386	35	224	20	306	27	111	10	57	5	32	3	1,116
Female subjects													
Caucasian	284	21	172	12	260	19	239	17	192	14	236	17	1,383
African-American	393	27	316	21	382	26	219	15	100	7	71	5	1,481
Mexican-American	381	25	270	18	444	29	225	15	117	8	86	6	1,523

Fig. 5.3 Demographics from NHANES III reference population. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Hankinson JL, Odencrantz JR, and Fedan, KB. *Spirometric Reference Values from a Sample of the General U.S. Population*. Am J Respir Crit Care Med 1999; 159:179–187. Official Journal of the American Thoracic Society

volunteered to undergo spirometry testing. No single reference equation is used universally, and the ATS/ERS 2005 guidelines do not recommend a particular reference equation. Rather, they recommend that each pulmonary function laboratory selects reference equations derived from a population that is similar to the patients tested by the laboratory [43].

The most widely used reference equations in the United States were derived from the National Health and Nutrition Examination Survey (NHANES III) and reported by Hankinson and colleagues in 1999 [43]. NHANES III was a random sample from the U.S. population of 20,627 individuals (including 16,484 adults). The study included an intentional oversampling of African-American and Mexican-American individuals (Fig. 5.3). Participants completed a health survey and collection of health data including standardized spirometry measurements. After excluding individuals with known or suspected lung disease and cigarette smokers, 4634 adults age 17–80 were included in the final dataset used by Hankinson to derive spirometry reference equations. Three separate equation sets were developed including Caucasian Americans, African-Americans, and Mexican-Americans. No equations were developed for Asian Americans because of lack of statistical power for that group.

The Global Lung Initiative (GLI) equations, published in 2012, are an effort to develop international spirometry reference equations [46]. The GLI authors pooled spirometry data at the individual level from previous studies of healthy asymptomatic nonsmokers, including data from NHANES III [43] and MESA [47]. The result was the largest yet single dataset of spirometry results from asymptomatic nonsmokers, consisting of 74,187 individuals across 26 countries. This dataset was then used to generate reference equations for calculation of percent-predicted normal spirometry values. Unfortunately, despite this great effort, the 2012 version of the GLI equations still are not universal spirometry equations as they did not include enough individuals from some parts of the world including Arab, Asian Indian, Polynesian, sub-Saharan African, and Latin American peoples [46].

"Race Correction" in Pulmonary Function Testing

Differences have been reported in comparing individuals of different ethnicity or race. Reference equations generally use age, gender, and height in calculation of predicted normal values. A few have race- or ethnicity-specific equations but most apply a multiplier or "race correction factor" for members of races or ethnicities other than the predominant group. Current ATS/ERS guidelines (2005) do recommend the use of "race correction" factors for interpretation of PFTs and recommend that self-identification be used to define a subject's race [45]. The 2005 guidelines state: "The subjects being tested should be asked to identify their own race/ethnic group, and race/ethnic-specific reference equations should be used whenever possible. If such equations are not available or are unsuitable for a particular setting, a race/ethnic adjustment factor based on published data may be used for lung volumes" [45]. This is based on the observation that variations in stature and environmental or socioeconomic factors do not fully explain the observed differences in lung function between racial/ethnic groups. The concept of "race correction" is problematic and controversial [48].

The NHANES IIIstudy found a difference in spirometry results by race and ethnicity (Fig. 5.4). The authors observed that the lower FEV1 values obtained from Mexican-Americans can be attributed to shorter heights, but that African-Americans have lower FEV1 values even after adjusting for height. The authors speculate that this may be due to difference in body build, only partly explained by the fact that African-Americans may have a smaller trunk-to-leg ratio than Caucasians, that is, a smaller trunk at any given height, hence smaller lungs. A subsequent analysis of NHANES data suggested that differences in SES and body habitus between Caucasians and African-Americans accounted for only about half of the observed racial difference in FEV1 and FVC [49]. On the basis of these observations,

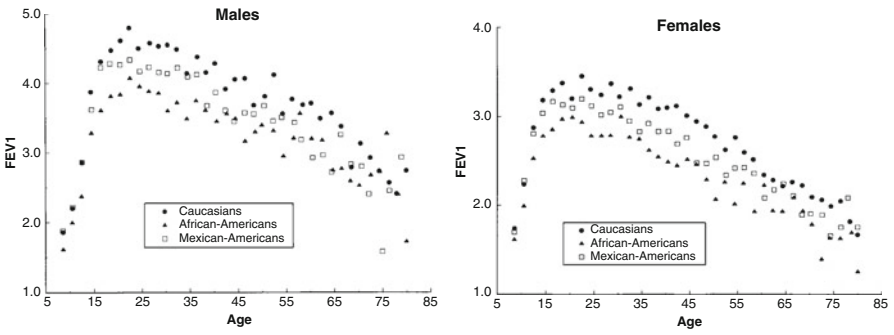

Fig. 5.4 Relationship between race and FEV_1 for men and women in asymptomatic nonsmokers from NHANES III reference population. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Hankinson JL, Odencrantz JR, and Fedan, KB. *Spirometric Reference Values from a Sample of the General U.S. Population*. Am J Respir Crit Care Med 1999; 159:179–187. Official Journal of the American Thoracic Society

Hankinson reported separate equations for Caucasians, African-Americans, and Mexican-Americans. The GLI authors observed similar findings. Lung function in the GLI dataset was similar between white Europeans and Mexican-Americans after correcting for height, and the GLI authors report a single reference equation ("Caucasian") for use with individuals from both groups. Among African-Americans, lung function was observed to be lower compared to "Caucasians" even after adjustment for height by a mean difference of 14.7 % for men and 13.8 % for women for FEV_1 [46].

The NHANES III survey population did not include enough individuals of Asian ancestry (Eastern or Southern) to assess the ethnic differences in lung function from these groups. Therefore, no separate NHANES equations are available for use in testing patients from these ethnic groups. For Asian-Americans, the ATS/ERS 2005 guidelines recommended using a correction factor of 0.94 applied to reference values obtained from the Caucasian equations [45]. Only two references are cited by the guidelines in support of this correction factor [50, 51]. One study examined 3076 elderly Japanese-Americans (ages 71–90) residing on the island of Oahu, Hawaii [51]. The other cited study was a small study sampling 80 medical students and physicians between age 22 and 33 that included 40 whites and 40 Asian-Americans [50]. The authors found slightly lower lung function measurements in Asian-Americans compared to whites after correcting for age, length of residence in the United States, activity level, baseline characteristics, and anthropometric measurements.

A correction factor of 0.88 was subsequently proposed for Asian-Americans based on results of the 2010 Multi-Ethnic Study of Atherosclerosis (MESA) Lung study [47] which evaluated spirometry in 1068 healthy nonsmokers. The study group was ethnically diverse, including 25 % white, 20 % African-American, 32 % Asian-American, and 23 % Hispanic (including roughly half Mexican and half non-Mexican Americans) individuals. The purpose of the study was to validate the NHANES III reference equations in a large multiethnic adult population. The NHANES III equations performed well when applied to the MESA-Lung patients who identified themselves as whites, African-Americans, and Hispanics. However, the authors observed that the NHANES III equations consistently overestimated lung function in Asian-Americans even when the 0.94 correction factor was used. They therefore proposed that a correction factor of 0.88 applied to the NHANES III equations for Caucasians should be used to achieve the best fit for Asian-Americans. The authors note that the MESA-Lung study population included primarily Asian-Americans of Chinese origin. Therefore, the observed difference in correction factor may be due to differences in lung function between Americans of Japanese and Chinese ancestry. No recommendation was made regarding patients of South Asian ancestry.

The GLI equations apply separate reference equations for Caucasians, African-Americans, North East Asians, and South East Asians. The GLI equations are the largest effort yet to generate accurate spirometry reference equations for individuals from Asia. Asia is a large continent with multiple ethnic groups, and predictably, analysis of the GLI dataset demonstrated that individuals from Asia could not be

pooled together as a single ethnic group. In particular, they observed differences in lung function between East Asians from the north and south. North East Asians were observed to have similar lung function to Caucasians while South East Asians had reduced lung function with a mean difference in FEV_1 of 9.7 % for men and 13.0 % for women compared to Caucasians [46]. The North East Asia group includes Koreans and Chinese from north of the Huaihe River and Qinling Mountains; while the South East Asia group includes Thailand, Taiwan, and the remainder of China including Hong Kong. There is insufficient data in the GLI population to generate reference equations for Japanese or South Asians (including India and Pakistan) and patients from these groups must use the "Other" ethnic group reference equations which are derived from a composite average of the reference equations from the four reported racial groups. These observations underscore the difficulty and uncertainties in race-based adjustment of reference values for PFTs.

Potential Causes for Disparities in Lung Function

From the initial NHANES III proposal of race-specific reference equations through the GLI equations, multiple studies have validated NHANES III findings of lower mean FEV_1 and mean FVC in African-Americans compared to Caucasians, as well as other race-specific equations [46, 47, 52]. A complete understanding of these racial differences in lung function remains elusive, but thorough investigation of prior study results may provide insight.

In 2001, Harik-Khan et al. examined 1242 white and 1084 African-American asymptomatic, nonsmoking adult participants from NHANES III to assess the racial difference in lung function after adjusting for anthropometric and socioeconomic factors such as sitting height, body mass index (BMI), poverty index, and educational attainment [49]. Socioeconomic indices were defined using level of education attained and the poverty index, where poverty index was defined as the ratio of family income in the last 12 months to the federal poverty line; therefore, a higher poverty index denoted a higher income and presumably SES. They concluded that about half of the racial difference in FEV_1 and FVC in both sexes could be accounted for by sitting height, poverty index, and level of education [49]. The remaining unexplained differences in lung function were speculated to be attributable to unmeasured environmental influences such as access to prenatal care, low birth weight, maternal smoking during pregnancy, air pollution, or other environmental exposures or, alternatively, to genetically determined differences in pulmonary development [49].

SES during childhood may be an important environmental factor contributing to the observed differences in lung function across racial groups. Its effect on young adult pulmonary function was examined in a study population extracted from the Coronary Artery (Disease) Risk Development in (Young) Adults (CARDIA) study [53]. Pulmonary function tests were collected at baseline (1985–1986), year 2, and

year 6, from 5113 participants ranging in age from 18 to 30 years. Childhood SES was measured from baseline self-reports of parental highest completed level of education [53]. Results showed a significant effect of childhood SES on pulmonary function at baseline and subsequent decline in lung function across young adulthood even after adjusting for anthropometric factors and current SES. Both young men and women from higher childhood SES had higher FEV_1 and FVC at baseline compared to those from lower childhood SES (Fig. 5.5) [53]. Moreover, in men, observed decline in FEV1 and FVC was steepest in those from lower childhood SES. In women, FEV1 decline was more rapid in participants from lower childhood SES, but there was no significant difference in FVC decline [53]. The authors concluded that individuals with lower childhood SES attained lower maximal pulmonary function as adults and also had faster and earlier onset of age-associated decline in lung function. These observations persisted even after controlling for the individual's current SES. The authors speculated that differences in environmental exposures and nutritional intake during childhood development may explain some of the study's observations [53].

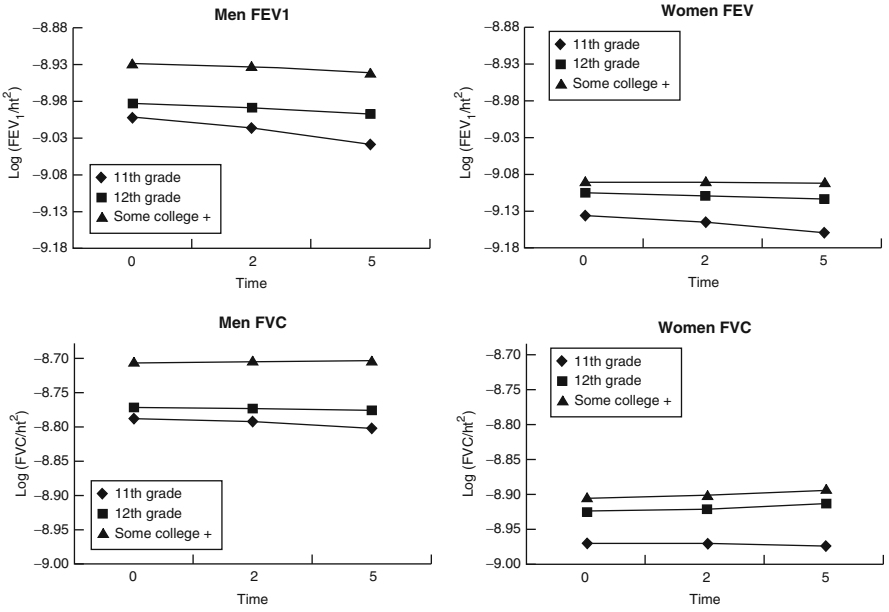

Fig. 5.5 Association between childhood socioeconomic status (SES) and pulmonary function over five years. Subjects divided into three groups by their parent's maximal educational attainment which is used as a proxy measure of their SES during childhood. Adjusted for initial pulmonary status, age, age^2, current SES, asthma (unconfirmed and confirmed), parental smoking status (maternal and paternal), participant smoking status. Reproduced with permission of Oxford University Press from Jackson B, Kubzansky LD, Cohen S, Weiss S, and Wright RJ. *A Matter of Life and Breath*: *Childhood Socioeconomic Status Is Related to Young Adult Pulmonary Function in the CARDIA Study*. Int J Epidemiol 2004; 33:271–278

Table 5.2 Socioeconomic status and exposure to poor air quality in the United Kingdom. In urban areas, households of lower socioeconomic status are more likely to live in areas with poor air quality [54]

Occupation of head of household	Urban households exposed to poor air quality (%)
Professional (I) or managerial (II)	67.5
Skilled Manual (IIIM) or nonmanual (IIIN)	71.8
Semiskilled (IV) or unskilled (V)	73.2

Air quality may be a significant and underappreciated environmental contributor to disparities in lung function. Wheeler et al. evaluated the effects of air quality and SES on pulmonary function in a population of 39,251 English participants ranging in age from 16 to 79 years [54]. Occupation of the head of household was used as a measure of SES with classes divided into six categories (in order of highest to lowest SES): I (professional), II (managerial), IIIN (skilled nonmanual), IIIM (skilled manual), IV (semiskilled), and V (unskilled) [54]. Air quality was extrapolated from 1996 annual mean pollutant concentration estimates over a defined geographic area. Pollutants measured included benzene, particulate matter, sulfur dioxide, and nitrous oxide. From these data, an air quality index quintile was computed for each residential postcode—quintiles 1–3 representing good ambient air quality and quintiles 4 and 5 poor ambient air quality. Results revealed urban households from the lower socioeconomic class were exposed to poorer air quality and had worse lung function (Table 5.2 and Fig. 5.6) [54]. Poor air quality had a negative effect on lung function even after adjusting for socioeconomic class. Limitations in this study included the use of 1 year's mean exposure to represent an assessment of total outdoor air pollution over the course of the study as well other potential confounding factors including other air pollutants such as ozone and possible occupational exposures [54].

Hegewald and Crapo sought to examine the effect of SES on lung function in children and adults by review of the medical literature [55]. They discovered adults and children from a lower SES had reduced pulmonary function. Smoking status contributed to this relationship, but did not fully explain the decline in pulmonary function in the poor, and most importantly, this relationship persisted in never smokers. The deleterious effect of low SES on lung function was concluded to be multifactorial as both male and female study participants of all ages in countries with various standards of living and environmental exposures mirrored these findings. Prenatal exposures, recurrent childhood respiratory infections, housing conditions (including proximity to highways), second-hand smoke exposure, air pollution, and poor nutrition were considered possible contributing factors [55].

The question of genetic versus environmental influence on lung function was tested in a 2010 study comparing pulmonary function in immigrant and US-born Asian Indians [56]. In this study, 462 healthy nonsmoking Asian Indian subjects 16–36 years in age living in the Chicago area were recruited from 1995 to 2005.

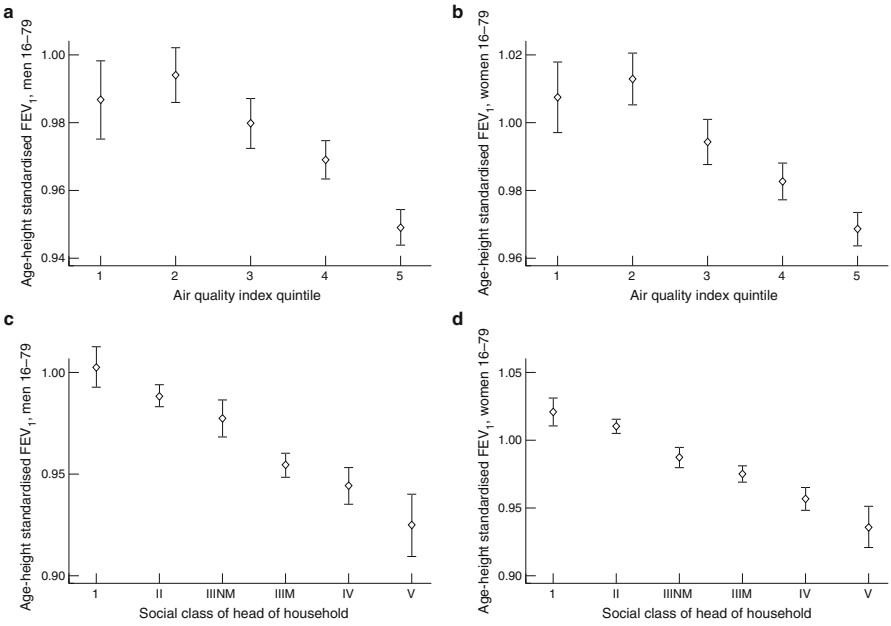

Fig. 5.6 Effect of ambient air quality index quintile and social class on FEV_1 in men and women. Social class categories (in order of highest to lowest SES): I (professional), II (managerial), IIIN (skilled non-manual), IIIM (skilled manual), IV (semi-skilled), and V (unskilled). Reproduced from Wheeler BW and Ben-Shlomo Y. *Environmental Equity*, *Air Quality*, *Socioeconomic Status*, *and Respiratory Health*: *A Linkage Analysis of Routine Data from the Health Survey for England*. J Epidemiol Community Health 2005; 59:948–954 with permission from BMJ Publishing Group Ltd

Immigrant Asian Indians were defined as subjects migrating to US from the Asian India subcontinent. US-born Asian Indians were born to Asian Indian parents and were raised in the US. For the same age and height, US-born Asian Indian men and women had higher pulmonary function values compared with Asian Indian immigrant men and women [56]. Prior studies comparing pulmonary function in US-born Japanese to Japanese immigrants have noted similar findings with US-born Japanese having higher pulmonary function than their Japanese immigrant countrymen [57].

The observed difference in US-born versus immigrant Asian Indians was hypothesized to be related to environmental, socioeconomic, or nutritional factors. Investigation of socioeconomic factors (education and income levels) revealed no difference between the groups; however, in both sexes, US-born Asian Indian subjects were taller than the immigrant study population. It has been noted in the developing world that poor growth in infancy (the first 1–2 years of life) and low birth weight lead to a reduced height with age [3, 56]. As economic conditions improve, individuals grow taller mainly due to an increase in leg length. This causes the ratio of sitting height to standing height to approach that of American Caucasians; hence,

establishing an association between the sitting height to standing height ratio and SES on lung function. This relationship provides a possible link between the effects of environment and nutrition on lung function [3, 44, 56].

Exploring the relationship between genetics and pulmonary function, Kumar et al. sequenced DNA from self-identified African-Americans [58]. The authors identified a series of genetic markers indicative of African ancestry and modeled for each individual a percentage of African ancestry. They found the percentage of African ancestry was inversely associated with lung function and, subsequently, created an ancestry-based model that proved to be superior to standard NHANES III models in predicting lung function [58]. They concluded that integrating individual genetic ancestry with normative equations for lung function in African-Americans may provide more accurate predictions than self-reported ancestry alone with acknowledgment that these observations may also be secondary to unmeasured confounding factors such as premature birth, SES, or environmental factors [58].

The impact of selection bias in modeling NHANES III reference equations and disproportionately excluding individuals of lower SES was investigated by Sickle et al. in 2011 [59]. He analyzed two study populations from NHANES III with acceptable and reproducible spirometry—the "restricted" group (the "healthy" patients use to model the NHANES III reference equations which excluded participants with prior tobacco use, physician-diagnosed respiratory disease, or respiratory symptoms in the last year; $N=2638$), and the "full" group (including these participants despite their exclusion criteria; $N=9658$). High school completion was used to measure SES [59]. Compared to the full group, the restricted group was younger, had a larger median FEV_1, and was more educated [59]. Figure 5.7 shows the cumulative distribution of FEV_1 by sex in the full and restricted group after adjusting for age and height [59]. FEV_1 was consistently higher in the restricted sample in both sexes, with the greater difference in FEV_1 occurring in men [59]. Figure 5.8 shows quantile regression estimates of FEV_1 adjusted for age and height from the full sample where African-Americans with less than high school completion represent the baseline [59]. Results show high school completion and Caucasian race are positively associated with increased FEV_1 in men and women across the full sample distribution. Additionally, high school completion has a more dramatic effect in Caucasians [59]. Based on these results, the authors suggested the unintended consequence in restricting the sample size was to create selection bias, and, consequently, underestimate the impact of SES on lung function [59]. Additionally, inclusion of smokers in the full sample likely contributed to the lower FEV_1 observation in the full sample; however, its significance could not be determined as NHANES III combined active smokers with prior smokers.

The prognostic value of FVC in predicting all-cause mortality in Caucasian and African-American participants from the Atherosclerosis Risk in Communities (ARIC) study was investigated by Burney et al. in 2012 [52]. In this study 15,792 participants were recruited, and 7489 (47.4 %) were asymptomatic, had usable spirometry, and complete data for confounding variable analysis (BMI, waist–hip ratio, sitting height, income category, current working status, most recent occupation, ever smoked, current smoking, pack-years of smoking, education level, and

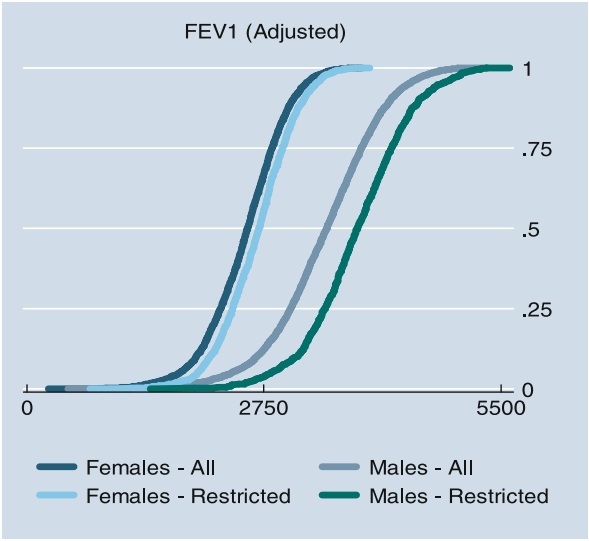

Fig. 5.7 Cumulative distribution of FEV_1 (adjusted for age and height) by sex from NHANES III cohort demonstrating higher FEV_1 in "restricted sample" compared to the "full sample." The restricted sample includes only asymptomatic nonsmokers and was the source for NHANES III reference equations. The full sample includes all subjects with acceptable spirometry. The exclusion criteria used to generate the restricted sample results in disproportionate exclusion of individuals of low SES compared to the full sample. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Sickle DV, Magzamen, S, and Mullahy J. *Understanding Socioeconomic and Racial Differences in Adult Lung Function*. Am J Respir Crit Care Med 2011; 184:521–527. Official Journal of the American Thoracic Society

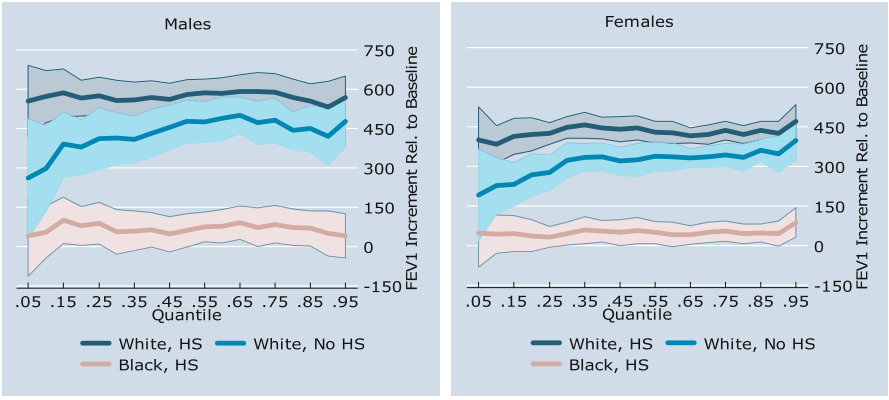

Fig. 5.8 High school completion, a proxy measure of socioeconomic status, is associated with increased FEV_1 for both whites and blacks. Conditional quantile regression estimate of FEV_1 increment (adjusted for age and height) relative to a baseline of black race with no high school (HS) completion using data from the NHANES III "full sample." Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Sickle DV, Magzamen, S, and Mullahy J. *Understanding Socioeconomic and Racial Differences in Adult Lung Function*. Am J Respir Crit Care Med 2011; 184:521–527. Official Journal of the American Thoracic Society

systolic blood pressure) [52]. The authors compared two ways of calculating the percent-predicted FVC in this population—either with the same equation used for all participants regardless of their race or with race-specific equations. Figures 5.9a, b and 5.10a, b show percent-predicted FVC calculated with the white-specific NHANES III equations applied to all participants; whereas, Figs. 5.9c, d and 5.10c, d show percent-predicted FVC calculated using the race-specific NHANES III equations [52]. The authors found that all-cause mortality increased with decreasing FVC in both genders and ethnic groups regardless of how FVC was calculated [52]. However, when the race-specific equations were used, an unexplained survival benefit was observed among whites compared with African-Americans with the same percent-predicted FVC (Figs. 5.9c and 5.10c). When a single set of equations was used for all participants, the percent-predicted FVC was associated with a similar mortality for both whites and African-Americans. The authors therefore suggested that the use of race-specific equations to calculate percent-predicted FVC could lead to underestimation of the prognosis and degree of respiratory impairment in African-Americans [52].

As demonstrated in this section, numerous studies have investigated the reasons for differences in lung function by race and SES. Unfortunately, making comparisons between these studies is difficult due to the lack of a uniform definition of race

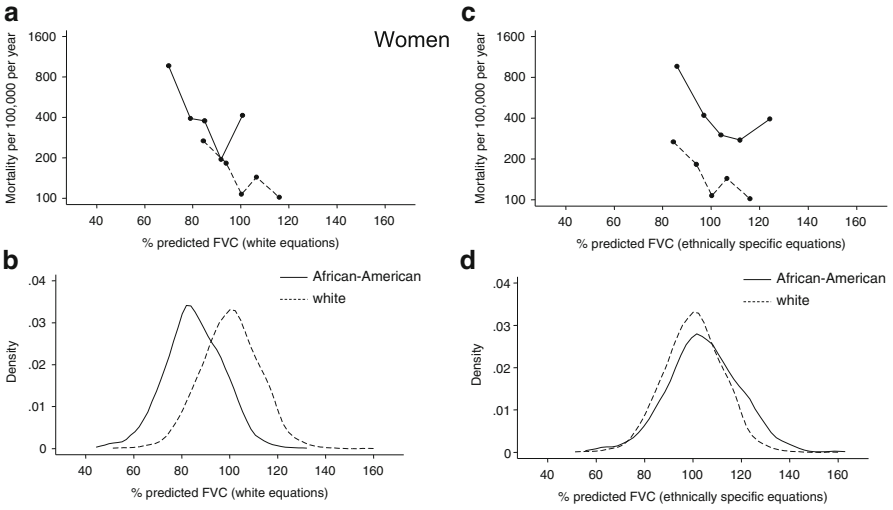

Fig. 5.9 Relationship between FVC and mortality from the ARIC study population (women). In the *left panel* (**a**, **b**), a single set of equations (NHANES white) is used to calculate percent-predicted FVC for all participants regardless of race. In the *right panel* (**c**, **d**), race-specific equations are used. When a single set of equations is used, percent-predicted FVC is associated with a similar mortality for both ethnic group. When race-specific equations are used, there is an unexplained difference in mortality between the two groups at the same percent-predicted FVC. Reproduced with permission of Oxford University Press from Burney PJ and Hooper RL. *The Use of Ethnically Specific Norms for Ventilatory Function in African-American and White Populations*. Int J Epidemiol 2012; 41:782–790

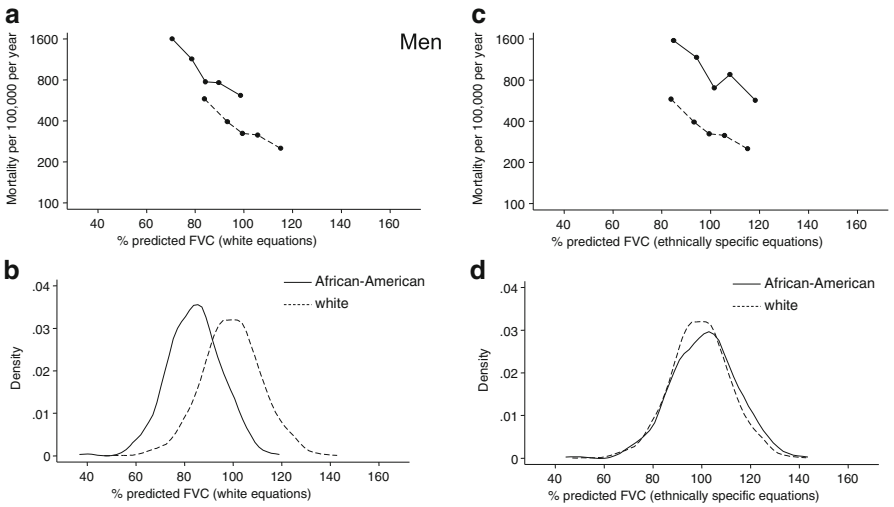

Fig. 5.10 Relationship between FVC and mortality from the ARIC study population (men). Just as in Figure 5.9, there is an unexplained difference in mortality between the two ethnic groups at the same percent-predicted FVC when race-specific equations are used. Reproduced with permission of Oxford University Press from Burney PJ and Hooper RL. *The Use of Ethnically Specific Norms for Ventilatory Function in African-American and White Populations*. Int J Epidemiol 2012; 41:782–790

and SES. Race has been defined by study participant, investigator, place of birth, or genetic analysis; whereas the parent's or participant's occupation, place of residence, income, or level of education has been used as surrogates for SES. Braun et al. proposed developing a consensus on the definition of race and ethnicity [60]; perhaps also to be considered is the need for a consensus defining SES. SES is broadly defined as a fusion of income, place of residence and housing, highest education level obtained, and occupation by Hegewald and Crapo [55]. The inclusion of multiple variables allows multiple factors to be considered as potentially influencing SES. The lack of a standard definition for SES leads to difficulty in translating and comparing results across studies.

A preponderance of evidence suggests that environmental factors have deleterious effects on lung development, and consequently, pulmonary function. The comparison of immigrant versus US-born Asian Indian pulmonary function provides strong evidence of the influence of environmental factors on pulmonary function [56]. Genetics also plays a role as Kumar et al. demonstrated an inverse relationship between percentage of genetically determined African ancestry and pulmonary function [58]. In considering the race-specific spirometric differences, the method of analysis may influence outcomes. Selection bias may unintentionally lead to underestimation of the effect of confounding variables such as SES contributing to observed differences across races [59]; however, overinclusiveness in defining study populations may result in lower spirometric reference values, which would be more specific but less sensitive in identifying pulmonary disease.

Controversies Associated with "Race Correction"

The use of "race correction" or race-based equations in the calculation of normal PFT values has generated controversy [60]. This is in the context of broader controversy about the use of race or ethnicity in biomedical research [61, 62]. Race has been used for many years in biomedical research as a crude proxy for genetic similarity between patient groups, but substantial limitations exist with this approach. Race and ethnicity are social constructs that do not have clear scientific definition [62]. The most commonly used racial classifications in biomedical research are derived from the U.S. Census, which includes five major groups: African-American, white, Asian, Pacific Islander, and American Indian.

Race in biomedical research is generally, but not universally, classified by self-report of subjects. It has been demonstrated among African-Americans that self-identified race is associated with an individual's predominant ancestral background [63]. However, there are significant limitations in the use of race in this manner. Admixture is not accounted for by this definition of race. Specifically, individuals who share the same self-identified race may vary widely in their percentage of African or European ancestry. The previously described study by Kumar illustrates the importance of admixture. The authors used genetic markers to calculate percentage of African ancestry in subjects who identified themselves as African-American [58]. They then examined FEV_1 of these patients in comparison with the percentage of African ancestry, finding an inverse linear association between FEV_1 and percentage of African ancestry (Fig. 5.11). This ancestry-based model was superior to standard NHANES III models in predicting lung function, and, furthermore, the percentage of genetic African ancestry was inversely associated with lung function in the three independent cohorts across a wide range of ages [58]. This supports the idea that genetic factors, independent of environmental factors such as SES,

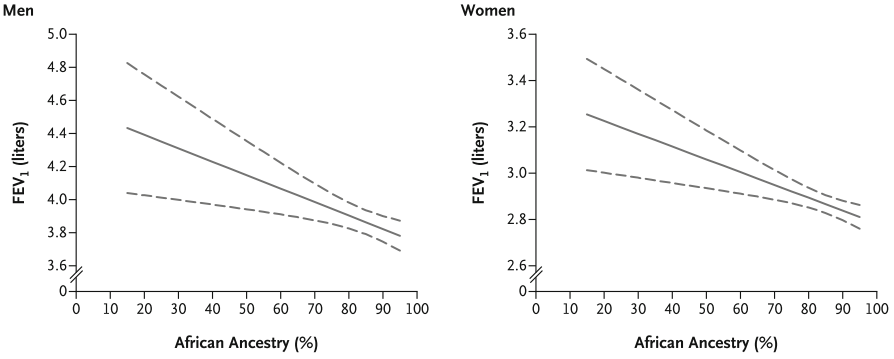

Fig. 5.11 Relationship between FEV1 and percentage African ancestry (estimated by genetic markers) in men and women. *Dashed line* 95 % confidence interval. From Kumar R, et al. *Genetic ancestry in lung-function predictions*. N Engl J Med 2010; 363:321–330. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

account for part of the observed differences in lung function between whites and African-Americans. This study also underscores the limitations of use of self-reported race without accounting for admixture. Supporters of race adjustment in pulmonary function have advocated that although race is an imperfect tool, the use of race correction results in more accurate estimation of lung function and that absence of race correction may result in misdiagnosis of disease and misclassification of the severity of disease [48]. In the future, more detailed genetic analysis may improve precision of the estimate of normal values for lung function.

Summary

Pulmonary function tests (PFTs) are necessary for the diagnosis and management of many lung diseases. The provision of high-quality PFTs requires access to facilities with specialized equipment and trained technicians. PFTs are underutilized, particularly in the care of underprivileged and elderly persons. The underprivileged, including minorities, non-English speakers, and individuals of low SES, may encounter numerous barriers to receiving high-quality pulmonary function results and appropriate interpretation of the results. Pulmonary function results are interpreted in the context of predicted reference values derived from large healthy populations that may not adequately reflect the diversity of the larger population for a variety of reasons. Poor quality PFTs, which are often misinterpreted as showing evidence of disease, are more common in the underprivileged and the elderly. Differences in lung function occur in relation to race and SES. Some, but not all, of these observed differences in lung function are attributable to anthropomorphic and environmental factors, but some remain and make the distinction of health from disease more difficult in these individuals than in the larger population. The use of race-specific reference equations or race correction factors improves the interpretation process, but further effort is needed to improve both the quality of tests and the ability to use the tests in clinical management and research.

References

1. National Asthma Education Prevention Program. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138.
2. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143–78.
3. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the third national health and nutrition examination. J Intern Med. 2003;254(6):540–7.
4. Han MK, Kim MG, Mardon R, et al. Spirometry utilization for COPD: how do we measure up? Chest. 2007;132(2):403–9.

5. Lee TA, Bartle B, Weiss KB. Spirometry use in clinical practice following diagnosis of COPD. Chest. 2006;129(6):1509–15.
6. Unequal treatment: confronting racial and ethnic disparities in health care (Book). Choice: current reviews for academic libraries. 2003;40(10):1780.
7. Carr W, Zeitel L, Weiss K. Variations in asthma hospitalizations and deaths in New York City. Am J Public Health. 1992;82(1):59–65.
8. El-Ekiaby A, Brianas L, Skowronski ME, et al. Impact of race on the severity of acute episodes of asthma and adrenergic responsiveness. Am J Respir Crit Care Med. 2006;174(5):508–13.
9. Gottlieb DJ, Beiser AS, O'Connor GT. Poverty, race, and medication use are correlates of asthma hospitalization rates. A small area analysis in Boston. Chest. 1995;108(1):28–35.
10. Gupta RS, Carrion-Carire V, Weiss KB. The widening black/white gap in asthma hospitalizations and mortality. J Allergy Clin Immunol. 2006;117(2):351–8.
11. Haselkorn T, Lee JH, Mink DR, Weiss ST. Racial disparities in asthma-related health outcomes in severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol. 2008;101(3): 256–63.
12. Ray NF, Thamer M, Fadillioglu B, Gergen PJ. Race, income, urbanicity, and asthma hospitalization in California: a small area analysis. Chest. 1998;113(5):1277–84.
13. Zhang X, Morrison-Carpenter T, Holt JB, Callahan DB. Trends in adult current asthma prevalence and contributing risk factors in the United States by state: 2000–2009. BMC Public Health. 2013;13:1156.
14. Walker PP, Mitchell P, Diamantea F, Warburton CJ, Davies L. Effect of primary-care spirometry on the diagnosis and management of COPD. Eur Respir J. 2006;28(5):945–52.
15. Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the lung health study. 1. Methods and quality control. Am Rev Respir Dis. 1991;143(6):1215–23.
16. Standardization of spirometry, 1994 update. American thoracic society. Am J Respir Crit Care Med 1995;152(3):1107–1136.
17. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
18. Johns DP, Burton D, Walters JA, Wood-Baker R. National survey of spirometer ownership and usage in general practice in Australia. Respirology. 2006;11(3):292–8.
19. Eaton T, Withy S, Garrett JE, Mercer J, Whitlock RM, Rea HH. Spirometry in primary care practice: the importance of quality assurance and the impact of spirometry workshops. Chest. 1999;116(2):416–23.
20. Schermer TR, Jacobs JE, Chavannes NH, et al. Validity of spirometric testing in a general practice population of patients with chronic obstructive pulmonary disease (COPD). Thorax. 2003;58(10):861–6.
21. Bellia V, Pistelli R, Catalano F, et al. Quality control of spirometry in the elderly. The SA.R.A. Study. SAlute respiration nell'Anziano = respiratory health in the elderly. Am J Respir Crit Care Med. 2000;161(4 Pt 1):1094–100.
22. CDC NIOSH. http://www.cdc.gov/niosh/topics/spirometry/sponsors.html. Accessed 31 July 2014.
23. Masa JF, Gonzalez MT, Pereira R, et al. Validity of spirometry performed online. Eur Respir J. 2011;37(4):911–8.
24. Agaku IT, King BA, Dube SR. Current cigarette smoking among adults—United States, 2005–2012. MMWR Morb Mortal Wkly Rep. 2014;63(2):29–34.
25. Eisner MD, Yelin EH, Henke J, Shiboski SC, Blanc PD. Environmental tobacco smoke and adult asthma. The impact of changing exposure status on health outcomes. Am J Respir Crit Care Med. 1998;158(1):170–5.
26. Brunekreef B, Holgate ST. Air pollution and health. Lancet. 2002;360(9341):1233–42.
27. Rice MB, Ljungman PL, Wilker EH, et al. Short-term exposure to air pollution and lung function in the Framingham Heart Study. Am J Respir Crit Care Med. 2013;188(11):1351–7.
28. Cakmak S, Dales R, Leech J, Liu L. The influence of air pollution on cardiovascular and pulmonary function and exercise capacity: Canadian Health Measures Survey (CHMS). Environ Res. 2011;111(8):1309–12.

29. Lee JT, Son JY, Cho YS. The adverse effects of fine particle air pollution on respiratory function in the elderly. Sci Total Environ. 2007;385(1–3):28–36.
30. O'Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol. 2008;121(5):1133–9. e1131.
31. Rabito FA, Carlson J, Holt EW, Iqbal S, James MA. Cockroach exposure independent of sensitization status and association with hospitalizations for asthma in inner-city children. Ann Allergy Asthma Immunol. 2011;106(2):103–9.
32. Romieu I, Meneses F, Ruiz S, et al. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am J Respir Crit Care Med. 1996;154(2 Pt 1):300–7.
33. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. N Engl J Med. 2002;347(20):1585–92.
34. Yergan J, Flood AB, Diehr P, LoGerfo JP. Relationship between patient source of payment and the intensity of hospital services. Med Care. 1988;26(11):1111–4.
35. Flores G. The impact of medical interpreter services on the quality of health care: a systematic review. Med Care Res Rev. 2005;62(3):255–99.
36. Bischoff A, Hudelson P. Communicating with foreign language-speaking patients: is access to professional interpreters enough? J Travel Med. 2010;17(1):15–20.
37. The National Culturally and Linguistically Appropriate Services (CLAS) Standards in Health and Health Care. http://minorityhealth.hhs.gov/templates/browse.aspx?lvl=2&lvlID=15. Accessed 31 July 2014.
38. Centers for Disease Control and Prevention (CDC): National Health and Nutrition Examination Survey (NHANES) Interpretation Guidelines (November 2006). http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/Interpretation_Guidelines.pdf. Accessed 31 July 2014.
39. Olmsted County Public Health Services Report: Olmsted County Community Health Needs Assessment. 2008. http://www.co.olmsted.mn.us/OCPHS/reports/CHS%20assessments/Documents/Community_Description.pdf. Accessed 31 July 2014.
40. Hardie G, Liu R, Darden J, Gold WM. Ethnic differences in methacholine responsiveness and word descriptors in African Americans, Hispanic-Mexican Americans, Asian-Pacific Islanders, and Whites with mild asthma. J Asthma. 2010;47(4):388–96.
41. Trochtenberg DS, BeLue R. Descriptors and perception of dyspnea in African-American asthmatics. J Asthma. 2007;44(10):811–5.
42. Trochtenberg DS, BeLue R, Piphus S, Washington N. Differing reports of asthma symptoms in African Americans and Caucasians. J Asthma. 2008;45(2):165–70.
43. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. Population. Am J Respir Crit Care Med. 1999;159(1):179–87.
44. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
45. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948–68.
46. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–43.
47. Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. Chest. 2010;137(1):138–45.
48. Scanlon PD, Shriver MD. "Race correction" in pulmonary-function testing. N Engl J Med. 2010;363(4):385–6.
49. Harik-Khan RI, Fleg JL, Muller DC, Wise RA. The effect of anthropometric and socioeconomic factors on the racial difference in lung function. Am J Respir Crit Care Med. 2001;164(9):1647–54.
50. Korotzer B, Ong S, Hansen JE. Ethnic differences in pulmonary function in healthy nonsmoking Asian-Americans and European-Americans. Am J Respir Crit Care Med. 2000;161(4 Pt 1):1101–8.

51. Sharp DS, Enright PL, Chiu D, Burchfiel CM, Rodriguez BL, Curb JD. Reference values for pulmonary function tests of Japanese-American men aged 71 to 90 years. Am J Respir Crit Care Med. 1996;153(2):805–11.
52. Burney PG, Hooper RL. The use of ethnically specific norms for ventilatory function in African-American and white populations. Int J Epidemiol. 2012;41(3):782–90.
53. Jackson B, Kubzansky LD, Cohen S, Weiss S, Wright RJ. A matter of life and breath: childhood socioeconomic status is related to young adult pulmonary function in the CARDIA study. Int J Epidemiol. 2004;33(2):271–8.
54. Wheeler BW, Ben-Shlomo Y. Environmental equity, air quality, socioeconomic status, and respiratory health: a linkage analysis of routine data from the Health Survey for England. J Epidemiol Community Health. 2005;59(11):948–54.
55. Hegewald MJ, Crapo RO. Socioeconomic status and lung function. Chest. 2007;132(5): 1608–14.
56. Fulambarker A, Copur AS, Cohen ME, et al. Comparison of pulmonary function in immigrant vs US-born Asian Indians. Chest. 2010;137(6):1398–404.
57. Massey DG, Fournier-Massey G. Japanese-American pulmonary reference values: influence of environment on anthropology and physiology. Environ Res. 1986;39(2):418–33.
58. Kumar R, Seibold MA, Aldrich MC, et al. Genetic ancestry in lung-function predictions. N Engl J Med. 2010;363(4):321–30.
59. Van Sickle D, Magzamen S, Mullahy J. Understanding socioeconomic and racial differences in adult lung function. Am J Respir Crit Care Med. 2011;184(5):521–7.
60. Braun L, Wolfgang M, Dickersin K. Defining race/ethnicity and explaining difference in research studies on lung function. Eur Respir J. 2013;41(6):1362–70.
61. Foster MW. Looking for race in all the wrong places: analyzing the lack of productivity in the ongoing debate about race and genetics. Hum Genet. 2009;126(3):355–62.
62. Schwartz RS. Racial profiling in medical research. N Engl J Med. 2001;344(18):1392–3.
63. Yaeger R, Avila-Bront A, Abdul K, et al. Comparing genetic ancestry and self-described race in African Americans born in the United States and in Africa. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1329–38.

Chapter 6
Health Disparities as They Relate to Medication Adherence

Sandra R. Wilson, Meghan Halley, and Sarah Knowles

Key Points

- Rates of medication nonadherence in respiratory disease are high.
- A number of factors have been found to influence medication adherence in respiratory disease including characteristics of the health care delivery system, physician–patient relationship and communication, disease and treatment regimen, and patient.
- Low adherence appears to be more prevalent among vulnerable populations who experience disproportionate disease prevalence and severity and face barriers to obtaining adequate medical care.
- There is moderately strong evidence that interventions which use more diverse components, such as case management, self-management education, and shared decision-making are more effective at improving adherence than brief intervention with little personal contact.
- There is somewhat weaker evidence that strategies that achieve significant improvement in adherence are associated with improvement in clinical outcomes.
- When targeting adherence interventions to vulnerable patients who are at risk of poor health outcomes, it is essential to recognize that the existing regimen for many patients with poorly controlled disease may not adhere to current treatment guidelines. Attempting to motivate patients to follow an inadequate treatment regimen is both inappropriate and unlikely to be successful in improving outcomes.

S.R. Wilson, PhD (✉) • M. Halley, Ph.D., M.P.H. • S. Knowles, Ph.D., M.P.H.
Palo Alto Medical Foundation Research Institute, 795 El Camino Real,
Ames Research Building, Palo Alto, CA 94301, USA
e-mail: wilsons@pamfri.org

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_6

- There is a need to replicate and extend promising adherence improvement interventions in respiratory diseases and to determine whether these interventions work as well in low-income and minority populations as in more advantaged populations.

Successful treatment of chronic disease depends upon patients' disease management behaviors, which are guided by the recommendations of their physicians and other health care providers. Adherence has been defined as "the degree to which patient behaviors coincide with the clinical recommendations of health care providers [1, p. S69]." However, adherence has multiple dimensions, and there is no consensus on measurement methods or criteria that define behavior as "adherent" versus "nonadherent." In chronic respiratory diseases, as in other chronic conditions, adherence to clinical recommendations often requires not only adherence to a medication regimen, but also to monitoring of symptoms and lung function, avoidance of environmental exposures that worsen the disease process or precipitate symptoms, and other lifestyle changes. For the purposes of this chapter, however, we will focus primarily on *medication* adherence. In that context, the term "nonadherence" encompasses not only underuse of medication (typically, failure to fill/refill prescriptions for medication intended to be used on a routine basis to control a disease process and/or failure to keep medications available when and where they are needed) but also medication overuse (e.g., of quick relief or "rescue" medication) [2] and improper medication administration [3].

Adherence Measurement Methods

Direct Measurement

Direct methods of measuring adherence offer the advantage of confirming that the patient obtained and administered the medication appropriately. Use of biomarkers indicating the level of a medication or its breakdown products in blood or other tissue is one direct approach. Theophylline blood levels, for example, were commonly measured when that medication was in widespread use because of the need to maintain the level of that medication within a relatively narrow therapeutic range. However, such markers are not available for all respiratory disease medications, and even when available, the measured levels may reflect other internal and external sources and influences, as well as the amount of medication used. Further, no one biomarker can assess adherence for all medications in a multidrug regimen, and measurement of even a single biomarker can be invasive and expensive [1, 4].

Directly observed therapy (DOT), which has been commonly used to assure adherence in the treatment of tuberculosis [5], is also a very direct approach to assessing adherence. However, DOT is infeasible for adherence measurement (or for improving adherence) in chronic, noninfectious diseases in which medications must be administered daily or more frequently over long periods of time [1, 4].

Indirect Measurement

Indirect methods of monitoring adherence are more commonly used in both research and clinical practice [1, 4]. Self-reported adherence is commonly used, even in many clinical trials of pharmacotherapy, because it is low cost, unobtrusive, and the data may be collected through a wide variety of instruments, such as diaries and the Medication Adherence Rating Scale (MARS) [6]. In theory, patient report could also identify intentional versus unintentional nonadherence, and thereby provide clinicians with guidance as to the appropriate response to nonadherence. However, studies comparing self-report to more objective measures have repeatedly found that patients overestimate/overstate their medication adherence [7–12], and therefore all self-report measures of adherence must be interpreted with extreme caution and are not recommended for research use. In clinical practice, most clinicians do not formally assess adherence, but instead rely on their clinical judgment to evaluate the patients' likely adherence [1, 13]. However, there is strong evidence that clinicians are unable to accurately assess the extent to which patients comply with their instructions [8, 14, 15], underscoring the need for systematic use of more objective adherence measurements.

Various indirect measurement methods offer a relatively simple, more objective, and low cost alternative to self-report [1]. Pill counts and canister weights have been two of the most commonly used adherence measurement methods, especially in research [1]. Electronic adherence monitoring devices (EMDs) are increasingly used as the standard against which more traditional measures are evaluated [16]. Medical Events Monitoring System (MEMS) devices (e.g., *TrackCap* or *SmartCap*) offer an alternative to traditional pill counts, though these devices are not applicable to inhaled medications, but are susceptible to deception through patient "dumping" prior to clinical/research visits [17, 16]. Many metered dose inhalers (MDIs) and dry powder inhalers (DPIs) now come with a built-in electronic monitor and offer a potential method for effective adherence measurement in clinical practice. However, the basic models only record actuation, not date and time, so the results of monitoring can be misleading if patients actuate the device many times in a row without medication actually being administered to their airways [4]. More complex EMDs that attach to an MDI are also available, some of which store the time and place of each actuation (thus revealing medication "dumping"), wirelessly transmit reports, and even remind patients to take their medication (e.g., SmartInhaler (Nexus 6, Auckland, New Zealand)) [4, 16]. Nebulizer chronologs (Forefront Technologies, Lakewood, CO) can record the total length of nebulizer treatment per use [18]. These more complex EMDs are increasingly used in research, but are medication and/or device specific, expensive, and currently impractical for routine clinical use. Further, even the best EMDs do not provide direct information on actual medication inhalation or deposition in the airways.

With the expansion of electronic pharmacy and health records, medication refill orders and pharmacy dispensing data are increasingly used in larger health care systems to monitor whether patients actually acquire the medications they are

prescribed [4]. This information source allows calculation of multiple types of indices to provide a comprehensive picture of adherence to the medication regimen [19, 20]. Such indices include, for example, the days' supply acquired as a proportion of days in a particular time period, gaps in medication availability, and even derivative measures that consider the strength of individual medications (referenced, for example, to canister equivalents of a standard ICS preparation), as well as the amount dispensed in a given time period (adherence), to produce a measure of the aggregate intensity of the regimen dispensed over a period of time [21]. A limitation of indirect measures, including refill orders, dispensing records, pill counts, and canister weights, is that they may overestimate actual use because a portion of the medication dispensed may not actually be used, not used correctly, not used by the individual for whom it was prescribed, or because patients may be prescribed multiple supplies of a medication to have available at a child's school or second home. In some cases, this second supply may only be used for acute problems [4].

Careful attention to the type of adherence measure used—and its specific benefits and limitations—is essential in order to accurately evaluate the reliability and validity of the results of research on medication adherence, which includes research on potential disparities in medication adherence and research on potential disparities in response to medication adherence interventions.

Criteria for Defining Medication Nonadherence

As noted earlier, the criteria for classifying individuals as adherent or nonadherent have varied widely, as evidenced by examination of the criteria used in studies included in a 2004 review of 50 years of research on treatment adherence for a range of medical conditions [22]. In some studies the criterion has been derived from evidence of the minimal extent to which a particular prescribed regimen must be implemented in order to obtain a specific (or any) clinical benefit. Arguably, such evidence provides the most defensible approach to defining adherence. More often, the criterion has been arbitrary and based on clinical judgment or convention, for example, that the patient should have used 80 % or some other proportion of the recommended amount of medication, or should have used the medication on at least some defined proportion of the recommended days over a given period of time. Other investigators have avoided dichotomous classification of patients as adherent or not, and instead have used a continuous measure such as the proportion of the prescribed amount of medication that was used in a given time period, or the proportion of the prescribed amount of medication that was dispensed to the patient, or a metric based on refill prescription rates. Such definitional and methodologic differences may reflect a lack of reliable information on dosing levels required to achieve either minimum or optimal clinical efficacy, differences in study purpose, and the difficulties of determining how much medication patients actually used. These differences are problematic in many respects, and complicate efforts to determine the sources of the observed variance in adherence rates between studies, medical conditions, and populations.

Rates of Medication Nonadherence in Respiratory Diseases

Notwithstanding the problems of assessing adherence, by almost any measurement method and criterion reported rates of nonadherence warrant concern. The 2004 review of 50 years of research on treatment adherence for a range of medical conditions found that, on average, 24.8 % of patients were, by the researchers' various criteria, nonadherent to medical recommendations regarding medications, diet, health care behavior, exercise, or appointment follow-up. Reported nonadherence rates ranged from 11.7 % for HIV disease to 34.5 % for sleep disorders. Reported rates of nonadherence to preventive screening, exercise, health behavior change, medical appointments, and dietary recommendations, which ranged from 28.0 to 40.7 %, were even higher than rates of nonadherence to medications (mean rate = 20.6 %) [22]. A more recent (2012) review done for the Agency for Health Care Research and Policy (AHRQ) concluded that, across many different diseases and conditions, the findings have been consistent that "20–30 % of medication prescriptions are never filled and that, on average, 50 % of medications for chronic disease are not taken as prescribed [23, p. 2]." Again, the definition of "not taken as prescribed" may differ among different researchers and for different types of diseases (e.g., TB, HIV vs. chronic noninfectious medical conditions).

Medication nonadherence in respiratory diseases appears to be at least as prevalent as nonadherence in other chronic diseases. In DiMatteo's 2004 review, mean nonadherence to physician recommendations in studies involving pulmonary diseases was 31.2 % [22]. Asthma patients have been reported to use, on average, only 20–50 % of the prescribed amounts of controller medication [4, 24, 25]. Rates of nonadherence to tuberculosis treatment are sufficiently high, and the consequences of incomplete treatment sufficiently serious, for public as well as the individual's health, that DOT is the recommended approach, even in settings in which 90 % of patients take the course of medications as prescribed [26].

Consequences of Medication Nonadherence in Respiratory Diseases

Medication nonadherence has substantial negative consequences across all chronic conditions [22]. It has been estimated that, due to lack of adherence to the physicians' recommendations, as many as 188.3 million medical visits (one-fourth of all medical visits other than checkups) are essentially wasted, at a cost of as much as $300 billion dollars a year [22]. The consequences of nonadherence, however, go far beyond the cost of visits whose prescriptions and/or advice are ignored. Nonadherence to prescription medications has been estimated to account for 125,000 deaths annually [27, 28], 10 % of hospital admissions, and 23 % of nursing home admissions [23, 28, 29]. Nonadherence to controller medications has been associated with poor asthma control and activity limitations [30] and also has been implicated in fatal asthma episodes [31].

Specific estimates of the financial costs and morbidity associated with nonadherence to treatment for respiratory diseases collectively do not appear to be available. However, it is estimated that asthma alone, which affects 8.2 % of adult Americans and for which effective treatment is available, was responsible for approximately 1.75 million emergency department (ED) visits (1 % of all ED visits) and hospitalizations in 2010 [32]. Bender and Rand [33] cite Iskedjian et al.'s (2002) estimate of the annual Canadian national cost of hospitalizations due to nonadherence to asthma controller therapy as exceeding US $1.6 billion [34]. In the US, a 2014 review of adherence and health care costs found that increased adherence was associated with lower rates of hospitalizations and lower overall health care costs in patients with COPD and asthma patients with past ED visits and hospitalizations [35].

High rates of adherence in medication efficacy trials are often achieved by careful patient selection and/or special efforts to motivate compliance. The results of such trials may lead to unrealistic expectations of medication effectiveness when treatment at the trial dosage is delivered in typical clinical settings to an unselected patient population or to patients with greater barriers to treatment adherence. Conversely, nonadherence among patients involved in clinical trials also may have an adverse effect on research to evaluate new respiratory therapies [7, 36]. Relatively high rates of nonadherence have been found, using objective measures, in clinical trials of medication therapy in asthma in patients supposedly selected for their willingness to adhere to the study protocol, and the common use of diary cards or other forms of self-reported medication use may result in a substantial (e.g., 30 %) overestimate of actual use and "Unrecognized non-adherence to therapy in research studies can lead to an underestimate of the pharmacologic effects of study medications, especially for outcomes more sensitive to dose response" [35]. In such cases, the efficacy of the medication may be underestimated, and/or the dose required for clinical benefit may be overestimated.

Causes of Medication Nonadherence

A number of factors have been found to influence medication adherence in respiratory and other diseases. In an extensive 2003 report detailing these factors, the World Health Organization (WHO) organized these factors into five domains: health care system/team related, disease, therapy, patient, and socioeconomic factors [37], resulting in the Multidimensional Adherence Model. There are varying levels of evidence with regard to the role of these factors in shaping medication nonadherence in respiratory disease.

Characteristics of the Health Care Delivery System

The health care delivery system can affect the success of the management of any chronic illness that requires ongoing monitoring of the patient's regimen, adjustment as appropriate, and patient engagement. Health care delivery systems built on

an acute care model impede successful chronic disease management, including respiratory disease. Patients who receive their primary care from EDs—disproportionately patients who are low income, of minority backgrounds, and uninsured [38]—are unlikely to experience the benefits of a chronic care model that focuses on long-term control. Only recently, and with the advent of P.L. 111–148, the Affordable Care Act (ACA), has a shift begun in the financing of health care in the US, on a broad basis, away from a traditional fee-for-service model and toward a system with financial incentives for reducing the utilization of services for acute exacerbations of chronic conditions. The ACA provides opportunities for reimbursement of providers for chronic disease management services and the development of chronic disease management programs (ACA §2717(a)), as well as for providing patient counseling and education for disease prevention and reduction of various health risks. The availability of coverage under the ACA may increase the likelihood that such programs are developed and are more widely available, including to low-income and minority patients. In addition, for many patients with chronic respiratory (and other) diseases, specialist evaluation is necessary for proper diagnosis and treatment, and access to specialty care has in the past been more limited for uninsured (predominantly low-income and minority) patients [39]. One survey of 6612 adults with asthma found that ICS underuse was significantly more likely to be reported by patients being treated by generalists compared to those receiving specialty care [40].

Characteristics of the Physician–Patient Relationship and Communication

In focus groups, patients have identified poor doctor–patient communication as a key barrier to medication adherence [41], and poor provider–patient communication has been associated with poor adherence [42, 43]. Among the specific communication deficiencies that can increase nonadherence are inadequate monitoring, failure to explain side effects, failure to analyze patient's medication-taking behaviors, and failure to address the patient's individual situation and preferences. In their very thorough review, Diette and Rand cite direct evidence from studies in asthma, as well as indirect evidence from studies in other diseases, that poor provider–patient communication may contribute to nonadherence to asthma controllers and overuse of rescue medications and to disparities in outcomes for patients with asthma [44]. They also identify specific mechanisms by which this may occur. Physician characteristics and behaviors that may impair relevant communication include unconscious biases, incorrect assumptions, and stereotypes about groups of patients (such as that they are noncompliant), and behavior that reinforces the stereotypes. For example, a brusque communication style—one dominated by close-ended questions, lacking in empathy, and that doesn't offer treatment options—tends not to encourage sharing of worries, beliefs, or opinions about treatment. This may result in the physician receiving less information from the patient. That lack of information, and/or a different presentation/description of symptoms in some

patient groups, may also result in mis/under-estimation of symptom severity, which can remain uncorrected if objective measurement of lung function is not employed. In the face of such uncertainty and/or misinformation, the physician may rely on heuristics as a basis for treatment decisions and tend to underprescribe or underdose. This in turn may result in a patient perception that the treatment is not efficacious, which would further impair treatment adherence. Patient characteristics such as low literacy, lack of disease-specific knowledge, negative/inaccurate beliefs about the disease or the treatments, culturally conditioned disease models, the use of alternative therapies, and negative feelings about or lack of a positive relationship with the provider can also impair communication between the patient and clinician. And finally, characteristics of the health care system may also negatively affect communication between physicians and vulnerable patients, by failing to provide patient-appropriate educational materials, presenting barriers to access that differentially affect low literacy/non-English-speaking patients, having time limitations on visits that encourage physician reliance on heuristics and discourage addressing or even asking questions about potentially more complex problems and circumstances, and nonuse of nonphysician providers and alternative care models that could assist in care, particularly for vulnerable patients. All of these communication factors would tend to decrease the likelihood that patients, in particular, vulnerable patients, would adhere to the recommended treatment.

Characteristics of the Disease and Treatment Regimen

Implementing recommended medical treatment for respiratory diseases presents some unique challenges to adherence for patients and their parents/caregivers. These challenges derive from the inherent complexities of these diseases, their treatment, and the length of treatment required, medication side effects and patient concerns about possible side effects, and differences in how rapidly different medications act to reduce/relieve symptoms. While most chronic diseases are treated with medication delivered orally or by injection, respiratory diseases (notably asthma and COPD) are commonly treated by medication delivered to the airways by inhalation. More complex and technique-dependent medication regimens are associated with higher rates of nonadherence [45, 46]. A patient with moderate asthma, for example, typically has at least two inhaler devices—one for a controller and one for quick relief medication. Having three devices is not uncommon (e.g., if a separate long-acting beta agonist/LABA is added), and an oral medication may be added as well in more severe disease. One study found that COPD patients averaged a total of 6.26 medications with various dosing schedules and modes of administration, with some patients using as many as 16 medications just to manage their COPD [47]. Delivery devices for inhaled medications differ widely and require different techniques for effective medication administration. In addition, each medication may have a different administration schedule and/or a pattern of use that has to be adjusted to changes in the patient's disease status [48]. Despite advances in breath-actuated devices, spacers, nebulizers, etc., and the use of combination preparations (e.g.,

inhaled corticosteroids plus long- or short-acting beta agonists or anticholinergics), improper administration/use is extremely common and can result in inadequate dose delivery to the smaller airways [49, 50].

In respiratory disease, adherence appears to be positively associated with medication taken only once daily, with oral nonsteroidal medications compared with inhaled corticosteroids [51, 52], and with combination ICS and LABA compared with ICS alone or both medications in separate inhalers [53–55]. There is also limited evidence to suggest that adherence is poorer when more frequent (e.g., qid) rather than less frequent (e.g., bid) medication use is prescribed [56–58].

As is the case for all chronic diseases, the long (and potentially indefinite) duration of treatment presents an additional challenge to adherence in asthma, COPD, and other respiratory diseases such as cystic fibrosis. In latent TB, as well, the standard treatment with isoniazid is 9 months, and this extended timeframe relative to other common infections presents a similar challenge to adherence [59]. In addition, the various medications used to treat respiratory diseases also differ in how immediately their benefits are apparent. Rescue medications such as albuterol provide a rapid sense of relief of obstruction, whereas anti-inflammatory agents that must be taken routinely, such as inhaled corticosteroids and leukotriene modifiers, do not provide immediate relief and may need to be continued when the patient is not having acute symptoms. These differences in the timeline to apparent benefit contribute to the underuse of ICS and overuse of rescue medication in asthma and COPD [2, 60].

Both actual side effects and patients' concerns and beliefs regarding potential side effects are known to affect adult patients' willingness to use respiratory disease medications [61, 62] and the willingness of caregivers to administer them to their children on a routine basis [63]. In the treatment of active and latent TB, serious side effects of antituberculosis drugs are common [64]. There is evidence that both pediatric [65] and adult TB patients [66] who experience side effects are less adherent to treatment. Finally, negative health beliefs regarding inhaled medications and steroids have been identified as a potential factor contributing to lower medication adherence [41], and holding negative health beliefs regarding inhaled medications is correlated with lower adherence [67, 68], including in studies using pharmacy refill records [63, 69] and electronic adherence monitors [70].

Characteristics of the Patient

While disparities in respiratory disease prevalence and morbidity between different population groups are well documented, disparities in medication adherence are not as clearly documented. Adherence is poor across *all* demographic and socioeconomic groups. However, evidence exists that low adherence is associated with some of the characteristics of vulnerable populations—populations who experience disproportionate disease prevalence and severity and face barriers to obtaining adequate medical care (including specialist care).

Age. Multiple studies have shown that older children—and particularly adolescents—are less adherent to medication than younger children [9, 22, 71–73]. Surveys of parents and children suggest that parents are often unable to accurately evaluate their child's medication adherence [74], and that parents and older children may have unclear expectations regarding each other's changing level of responsibility in maintaining medication adherence [75]. For example, one study of African-American adolescents found lower adherence rates among families when parents and their children each believe the other is primarily responsible for medication adherence [76].

Several studies suggest that adherence rates are particularly low among elderly asthmatics [24, 77], although further research is needed to clarify the exact nature of this association. Characteristics of elderly patients that potentially contribute to poor adherence include diminished cognitive and motor skills necessary to follow complex medication regimens and use complex drug delivery devices [24, 50, 78], as well as high rates of comorbidities and poly-pharmacotherapy, and heightened concern about and/or experiences of side effects due to drug interactions [79–81].

Gender. Adherence does not appear to be reliably influenced by gender in adult populations. While some studies have found males with asthma to be more adherent [82], others have found females to be more adherent [40], and still others have found no gender difference [22, 42]. A systematic review and meta-analysis of adherence in chronic diseases (including respiratory diseases) concluded that female pediatric patients are more adherent than males [22]; however, a recent systematic review of studies in pediatric asthma did not find sufficient evidence to confirm this association [75].

Knowledge, Health Literacy, and Formal Education. The evidence of an association between asthma knowledge and level of medication adherence is limited [43], but many studies have shown that higher or increased knowledge about asthma and asthma medications do not necessarily translate into better or improved adherence [9, 71, 73, 83–85]. The evidence that low health literacy is associated with poor adherence is also equivocal. Two recent systematic reviews [86, 87] found only moderately strong evidence of an association between health literacy and medication adherence, but neither included studies in respiratory diseases [86]. A recent study examining the relationship between health literacy and medication adherence in asthma found such a relationship in an unadjusted analysis, but this association diminished after controlling for age, sex, and race/ethnicity [88]. There is stronger evidence in support of an association between medication adherence and more years of formal education [42, 46]. Education, however, is typically correlated with income, race/ethnicity, and other markers of socioeconomic status (SES) discussed below. One study that examined the relationship between adherence and these commonly confounded factors found education was a stronger predictor of adherence than were race and income [42].

Income, Insurance, and Socioeconomic Status (SES). The evidence regarding the relationship between SES and adherence is mixed, with some studies reporting lower adherence among lower SES patients [22, 42, 46, 77], and others finding no

association [8, 9, 71, 89]. Comparison across studies is difficult because SES may be measured at the individual or household level, and may be based on a range of factors, including income, educational status, race/ethnicity, employment, and/or other variables. A systematic review found that adherence is more clearly associated with income than with other measures of SES, but did not find an association between income and adherence in studies of asthma or COPD [22]. However, cost of medications clearly plays a role in nonadherence. One study in a national probability sample of over 16,000 Medicare (> age 65) patients found that higher out-of-pocket costs of inhaled medications were associated with particularly high rates of cost-related medication nonadherence [90]. Similarly, a systematic review of the literature on patient cost sharing and medication adherence found that, as patients' share of medication costs increased, adherence decreased [91]. Lack of medical insurance also has been associated with poorer adherence in the treatment of latent tuberculosis [66]. However, studies in populations with uniform health insurance and pharmacy benefits have continued to find variation in adherence [46], suggesting that financial barriers alone cannot explain lower adherence rates.

Comorbidities. Multiple studies have found evidence that patients with more comorbidities are more likely to be nonadherent [46, 77, 92]. A variety of factors may be involved, including financial barriers resulting from the fact that multiple comorbidities are likely to require more medications and hence greater out-of-pocket costs and the fact that multiple medications increase the complexity of the patient's overall medication regimen, and greater complexity, as noted earlier, is associated with lower adherence. With regard to specific comorbidities, depression is associated with lower adherence to asthma medication among adult women [92]. Asthmatic children with behavioral difficulties have been found to be less adherent with asthma medication [89]. For children, higher levels of parental stress and poorer parental mental health [8], as well as higher levels of reported family dysfunction [9] all appear to be associated with poorer adherence. These and other comorbidities also are more prevalent in vulnerable populations [93, 94].

Race/Ethnicity. Poor adherence is observed in virtually all studies of adherence in chronic diseases regardless of the racial or ethnic composition of the study population. To evaluate disparities in medication adherence rates, valid comparative studies using appropriate samples and analytic methods are required. Many cross-sectional comparative studies have reported such disparities in a wide range of diseases. African-American US Veterans Administration patients with hypertension are less likely to have well-controlled blood pressure, more likely to be less literate, and less adherent to their BP control medication regimen than whites [95]. A study using a 5 % sample of US Medicare beneficiaries found that adherence to heart failure medication was 63 % in Whites, 57 % in Asians, 53 % in Hispanics, 50 % in Native Americans, and 52 % in African-Americans and among Medicare survivors of myocardial infarction, adherence to β-blockers was 59 %, 54 %, 52 %, 47 %, and 43 %, respectively [96].

Studies of ethnic disparities in medication adherence in respiratory diseases are less numerous than such studies in cardiovascular diseases or diabetes and, to the extent that they do exist, they focus primarily on asthma. Such studies in both chil-

dren and adults have reported lower medication adherence in minority subgroups, even after adjusting for covariates such as education and income [46], and include studies that use electronic monitors to measure adherence [9, 71].

Despite the documented association between minority status and adherence, minority status may reflect a range of both personal internal factors (i.e., knowledge, attitudes, beliefs, and other psychological factors) and external factors (i.e., barriers to receiving care, doctor–patient communication, environmental stressors, etc.) leading to increases in intentional and/or unintentional adherence in these populations [97]. Evidence from studies in HMO patient populations with uniform insurance and pharmacy benefits, noted earlier, suggests that minority status remains associated with adherence, and that health insurance alone does not explain the difference in adherence by race/ethnicity [46, 82, 98]. Another study using pharmacy records found that among African-Americans, residential crime rates were negatively associated with ICS adherence, suggesting an environmental exposure potentially affecting adherence among minorities [98]. There is also emerging evidence that lower health literacy may at least partially explain racial disparities in health outcomes [86], though more research is needed. One study in elderly African-American and White asthma patients on Medicare examined self-report of running out of medications before filling them, failing to following physicians' instructions, and forgetting to take medications. After controlling for potential confounding factors, African-American race was only associated with not following physician instructions on how to take medication [99].

Another proposed explanation for the association between minority status and poor adherence is the potential impact of negative health beliefs on adherence [100]. One study that examined the relationship between minority status, health beliefs, and poor adherence found that negative beliefs about asthma therapy were more prevalent among minority patients and partially mediated the relationship between minority status and adherence to therapy [101]. Another study using pharmacy records found that accounting for "internal factors" (i.e., patient beliefs, knowledge, and motivation regarding asthma and asthma medications) diminished the association between race ethnicity and adherence [97]. However, further research is needed to confirm this relationship, as negative health beliefs—and particularly fear of adverse medication effects, belief that the asthma medication does not help or is not necessary, and the sense of only an intermittent need for medications—appear to be an important determinant of poor adherence in all patient groups, not solely minority patients [70, 102].

Effectiveness of Adherence Improvement Interventions

Since Haynes' seminal systematic review in 1987 [103], its periodic updates (most recently in 2014 [104]), several other independent systematic reviews [23, 105, 106], and two meta-analyses [28, 107] have been published that have critically examined the evidence of whether medication adherence in chronic diseases can be

improved, and have attempted to identify successful intervention strategies and intervention components. These efforts have also assessed the evidence that such interventions improve *clinical outcomes* as well as adherence, and the evidence that observed improvements in clinical outcomes are mediated by adherence improvements. These reviews encompass studies of adherence interventions in respiratory diseases (asthma, chronic obstructive pulmonary disease/COPD and, in some reviews, tuberculosis) but also adherence in other diseases including diabetes, hyperlipidemia, hypertension, depression, heart failure, and other chronic conditions. More focused reviews also have been carried out of interventions in asthma [108], COPD [109, 110], latent tuberculosis/TB [111], cystic fibrosis/CF [112], and other disease areas as well. Rather than add to these reviews, it seems more useful to consider their general conclusions about the effectiveness of medication adherence interventions in respiratory disease. We will focus especially on the evidence that has accumulated concerning the effectiveness of medication adherence interventions in asthma, since that disease has been most extensively studied. We will also consider methodological features of the original research studies and of the reviews that have implications for future research to develop effective adherence interventions.

Overview of the reviews. All but one [106] of the systematic reviews to date, as well as the meta-analyses, have restricted their scope to evidence provided by randomized controlled trials (RCT) in order to ensure that the study results would support a causal interpretation of any observed relationships between the intervention and study outcomes. With the exception of one review that only considered patient reminder systems [108], most reviews have considered a wide range of different approaches and combinations of approaches. None have included studies of financial or other incentive strategies, which typically have been utilized, with some success, to motivate/enable medication adherence in chronic infectious diseases such as TB and HIV/AIDS [113]. In most cases, the reviews have been restricted to studies involving adult patients, who make up the majority of patients with chronic diseases. Where studies of pediatric patients have met the inclusion criteria of specific reviews, they have primarily been studies in adolescents with asthma, the most prevalent chronic disease in children.

Studies included in these reviews have recruited their patient populations from both health care settings (private practices, large health care systems) and/or the community at large and from diverse racial/ethnic backgrounds and both genders. Very few studies have reported the effectiveness of their intervention in subgroups defined by income, education, or race/ethnicity, and have typically had limited power to make such comparisons. A few studies exclusively targeted low-income and minority patients. The recent review by Hu et al. [106] specifically addressed the evidence concerning the effectiveness of interventions to increase medication adherence in African-American and Latino populations, and considered studies eligible for that review if at least 75 % of their sample consisted of patients from a particular ethnic minority group or if appropriate comparative analyses were carried out. This review included both RCT, quasi/preexperimental, and observational

study designs, with sample sizes ranging from 10 to 520 (median 126). Four of the 36 studies involved asthma and three involved tuberculosis patients [106].

TheAHRQ review. The very ambitious 2012 review carried out for the Agency for Healthcare Research and Policy (AHRQ) [23] identified 62 studies published between 1994 and 2011 that met its selection criteria. The majority of these studies concerned hypertension, depression, hyperlipidemia, and diabetes, which share some features with chronic lung diseases (e.g., the need to continue treatment through periods when no symptoms are apparent), but studies in asthma and COPD were included as well. Studying intervention strategies that have been tested across many different diseases may identify generally effective strategies. However, it also is important to focus on particular diseases, considering what research has been done, what strategies have been evaluated, and what strategies have been shown to be effective or ineffective in those diseases, since unique features of different diseases may influence their findings. Respiratory diseases, in particular, have unique features related to the use of inhaled medications, and there have been historical changes in treatment (e.g., inhaled medications replacing oral theophylline), in conceptualization of the diseases (e.g., the shift in asthma from severity to level of control as the basis for treatment in all but newly diagnosed patients), and in other features that have implications for study design (e.g., the significant potential for misdiagnosis in and between asthma and COPD that necessitates confirmation of the diagnosis as an eligibility criterion). Such temporal changes need to be considered when evaluating findings of adherence intervention studies, especially those done two or more decades ago, but have been ignored in most reviews.

Eight of the 62 studies identified by the 2012 AHRQ review targeted lung disease. Seven focused exclusively on asthma; [21, 114–119] one included both asthma and COPD patients [120]. Studies involving infectious diseases, including tuberculosis, were excluded from the review. The interventions tested in these studies varied substantially in their approaches and intensities of intervention. One utilized two to three 5-minute automated interactive voice response (IVR) contacts with patients to assess symptoms, provide educational messages, and encourage refill of asthma controller medications and communication with their providers [114]. Another utilized a 30-minute audiotape or an educational booklet or both [118]. Others provided individual patient medication refill history and other medication use data to pharmacists [120] or clinicians [119] along with guidance for the use of this information in counseling or caring for patients. Patients whose pharmacists received and utilized the information on patients' refill history were supplied with a peak flow meter and instructions on its use, and the study design allowed for determination of the effect of the peak flow meters alone [120]. It was intended that these interventions would lead the clinician to communicate with the patient to encourage his/her adherence to the existing regimen. While this)was not an intended outcome, the interventions in which physicians [119] or pharmacists [120] were given information on patients' refill history could have resulted in changes in the patients' medication regimens, but this was not mentioned as a possibility in the publications or review.

Several studies utilized self-management education, delivered, variously, in one 30-minute individual session conducted by an advanced practice nurse, plus two 30-minute individual reinforcement sessions with the study coordinator [116, 117], six weekly 2-hour group sessions [115], or as a part of one individual session with an asthma care manager that lasted, on average, ~1-1/4 or 1-2/3 h, depending on whether the patient was randomized to a traditional clinician decision-making approach to the selection of a treatment regimen or to a shared decision-making approach, respectively, plus a 30-min follow-up session a month later, and up to three brief follow-up phone calls 3, 6, and 12 months after session 1 (~10 min each) [21]. This was the only study in which the adequacy of the patient's medication regimen was directly addressed in the intervention and one of the few that specifically targeted patients with poorly controlled disease.

The follow-up periods in the respiratory disease studies reviewed by AHRQ ranged from 6 weeks to 2 years and the sample sizes varied widely. The minimum sample size of studies included in the AHRQ review was 40. However, this minimum did not take into account the study design or planned comparisons. One 4-arm study with a total of 46 patients had only 10–13 participants per comparison group in the analyses [118]. No significant differences were found, perhaps because the study appears underpowered to detect group differences. In contrast, another study randomized 36 pharmacies to three study arms/conditions ($n=12$ each) and had a total patient sample size of 1113 [120]. Follow-up retention at the final (12 month) assessment was high (81 %), and since pharmacy identity proved not to be a significant source of variance (i.e., there was no cluster/design effect), the effective sample sizes in the patient-level analyses were $n=447$ (pharmaceutical care program group), $n=363$ (peak flow monitoring control group), and $n=303$ patients (usual care control group). Two 2-arm studies [116, 117] had samples ranging from 25 to 45 per group; one 3-arm study had a total sample size of $n=612$ ($n=204$ per group) [21]. The first two of these studies reported significant effects on both medication adherence and at least one clinical outcome; the third reported significant effects on multiple outcomes compared with the usual care control group. While some of the smaller studies may have been underpowered to detect improvements in their primary and secondary outcomes, large sample size was not necessarily associated with positive results. The two reasonably large studies that provided feedback to pharmacists or physicians on patients' medication adherence failed to find intervention-related evidence of improved adherence and found that the adherence of the clinicians to the intervention-recommended activities at the patient level was extremely poor [119, 120].

Considering the evidence across multiple medical diagnoses, the conclusions of the earliest reviews primarily focused on the scarcity of well-designed trials, the spotty picture of positive and negative results, and the reliance, in many studies, on patient-reported adherence as an outcome. Over time, the quality of the research has improved, including the use of objective measures of adherence. More recent reviews, such as the one done for AHRQ [23], came to more positive conclusions, and there appears to be a general consensus that: (1) there is moderately strong evidence, at least in some disease areas (notably asthma) that interventions that utilize

more diverse components, such as case management, self-management education, and shared decision-making, appear to be more effective than brief interventions with little personal contact, (2) there is somewhat weaker evidence that strategies that achieve significant improvement in adherence are associated with improvement in clinical outcomes, and (3) additional analyses and research are needed to determine whether improved adherence mediates the improved clinical outcomes.

The AHRQ review concluded that, "Collectively, the most consistent evidence was that various types of interventions improved medication adherence outcomes for hypertension, heart failure, depression, and asthma. These improvements were accompanied by … improved symptoms, pulmonary function, health care utilization, and quality of life for shared decision making for asthma patients…" With regard to the specific intervention component of involving the patient in decisions about their regimen, the review concluded that one study [21] "demonstrated that shared decision making (in which non-physician clinicians and patients negotiated a treatment regimen that accommodated patient goals and preferences) had a greater effect on adherence to asthma medications than did a clinician decision making approach (in which the non-physician clinician prescribed treatment without specifically eliciting patient goals or preferences). Both approaches were more efficacious than usual care. The effects of shared decision making on adherence lasted up to 2 years, whereas those attributed to clinical decision making had attenuated at that point" [23]. The latter statement is somewhat inaccurate in that the study's measure of adherence (the cumulative medication acquisition index) decreased in both conditions in the second follow-up year, although perhaps not on the same time course. It was the strength of the medication regimen (in canister equivalents of beclomethasone), that persisted into the second follow-up year, due in part to the somewhat stronger regimens selected when patients participated in the shared decision-making process.

The AHRQ review also considered the effectiveness of *policy-level* interventions (i.e., reductions in out-of-pocket expenses for prescription dru)gs) to improve medication adherence was reasonably strong across clinical conditions, but the only study that looked at inhaled corticosteroid (ICS) use in asthma and COPD found no effect. The fact that this strategy, which specifically addresses a barrier to adherence for low-income, uninsured patients, has been effective in other diseases and with other medications suggests a need for further research to determine whether it is consistently ineffective with ICS medications and, if so, what the explanation might be.

Potential Unrecognized Sources of Variability in Adherence Intervention Study Results

The variability in results of adherence intervention studies in the past has been largely assumed to come from variability in the measures of adherence and in the intervention strategies themselves. However, a significant portion of the variability

in the results of studies reviewed by AHRQ and others, and hence the possible perception that strong evidence that medication adherence and clinical outcomes can be improved is lacking, may result from characteristics of the study samples and from a fundamental difference among intervention strategies that has not received attention in systematic reviews or meta-analyses.

Failure to confirm disease diagnosis. Only three of the studies of respiratory disease reviewed by AHRQ required confirmation of the diagnosis as an inclusion criterion [21, 116, 117]. Such confirmation is considered requisite in asthma clinical trials [121] and is a concern in COPD and other respiratory conditions as well. Basing eligibility on a patient-reported doctor diagnosis of asthma, for example, or even on an asthma diagnosis encountered in the patient's medical record, risks inclusion of patients with fixed airway obstruction and/or COPD, or some other condition that has been misdiagnosed as asthma. Such patients would be much less likely to show clinical improvement when treated with asthma medications, even if their medication adherence was improved. Moreover, the failure to benefit from the treatment regimen, in the past or as a result of attempted use consequent to the intervention, would not be expected to motivate adherence in such patients.

Lack of focus on the appropriate target population. Even more fundamentally, the inclusion and exclusion criteria of most of the existing evaluations of adherence improvement interventions in respiratory diseases do not clearly target the patients who stand to benefit from an adherence intervention. We suggest that *it is patients whose chronic disease is poorly controlled who warrant intervention*, as shown in Fig. 6.1. Those whose chronic disease is well controlled on their present medication regimen, even if they are not "adherent," do not appear to warrant either medical or adherence intervention, unless the goal were to be to determine whether therapy might be stepped down, without loss of control, to minimize possible side effects. The level of adherence of patients whose disease is well controlled is not a primary concern.

For patients with poorly controlled asthma, medical treatment guidelines advise clinical intervention and stepping up therapy [48]. But it is also recommended that, before doing so, the possibility of medication nonadherence should be considered, and, if present, addressed. If the patient is determined to be adherent, then evaluation of the patient's regimen and other factors that may be affecting control is in order. Because a change in regimen may lead to subsequent adherence issues, the use of strategies that lead to better adherence is clearly warranted. Patients with disease that is not well controlled and who are nonadherent to their regimen are clearly the primary target population for an adherence intervention (as illustrated by the lower right quadrant in Fig. 6.1), including attention to the regimen and the patient's goals and preferences. However, in the same sense that a decision to step up therapy should not be undertaken without considering whether nonadherence to the current regimen may be compromising its effectiveness, an adherence intervention is arguably inappropriate in patients with poorly controlled disease unless it is known, or can be assured by the intervention process itself, that the regimen to which the patient is expected to adhere is consistent with accepted medical guidelines

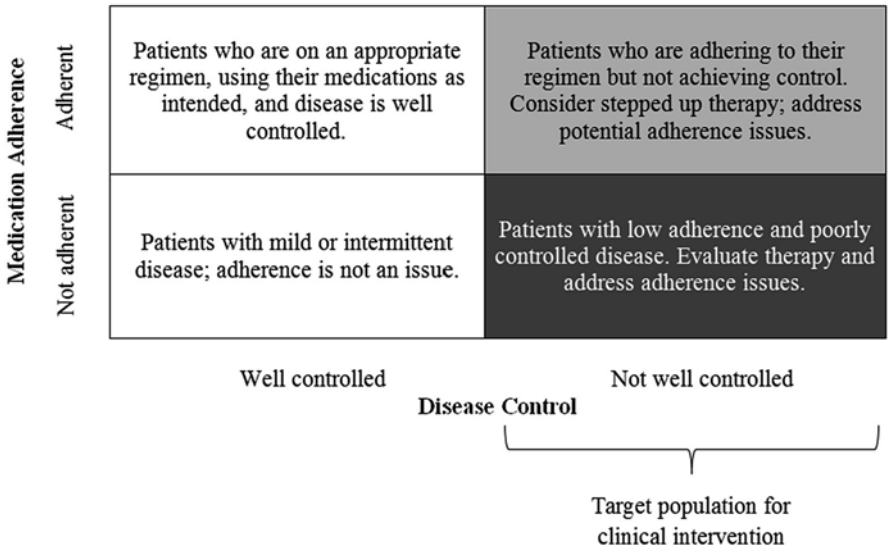

Fig. 6.1 Classification of patient population relative to control and medication adherence

and appropriate for that patient. Attempting to motivate patients to adhere to an inadequate or potentially inadequate treatment regimen, using strategies that are isolated from the patients' medical care is unlikely to be successful in improving adherence, especially when that care is discontinuous or inadequate in some other respect. Ignoring the possibility of deficiencies in patients' regimen (as is the case in adherence interventions that do not involve personal contact with the patient) does not make these problems go away and may be one reason why such interventions have not demonstrated much success in terms of clinical improvement [109].

In research to evaluate adherence interventions, the vast majority of studies have not selected patients whose disease was poorly controlled. Instead, studies have used other eligibility criteria, such as patients who were prescribed an ICS or other asthma controller medication within some preceding time period or patients who had asthma of some particular severity level (mild-moderate, for example, in one study, or moderate-severe in another). This is understandable in studies carried out prior to the clarification of the distinction between asthma severity (applicable to treatment-naïve patients) and asthma control (applied to treated patients), and prior to the development of straightforward instruments and procedures to assess control. However, even more recent adherence intervention studies have not always defined their target population clearly or chosen their eligibility criteria appropriately for that target. The implicit assumption may have been that this is unnecessary because patients' adherence will be poor, as it so often is. However, not focusing on the appropriate target population has resulted, in some studies, in the recruitment of patients with relatively high adherence at enrollment and/or relatively well-controlled disease (FEV_1 ~80 %; low symptom level), and may have decreased the

likelihood that any clinical benefits would be detected. While, from a study design perspective, the adequacy of the treatment regimen might be addressed during a run-in period and prior to randomization and delivery of an intervention of interest, we would suggest that it is more appropriate to integrate reexamination of the patient's regimen in relation to their level of control into the adherence improvement strategy itself.

There is a further potential problem. In carrying out research on interventions that use strategies that place intervention personnel in direct contact with the participants but that do not directly address the patient's medication regimen, the possibility exists that the interventionists may become aware of problems in a patient's regimen or medical care, and this can put them in an uncomfortable conflict between their responsibility not to deviate from the research protocol and their responsibility to the individual patient.

The fact that both the shared decision-making and clinician decision-making care management interventions in the study by Wilson et al. [21] were associated with clinically and statistically significant improvement in clinical outcomes relative to usual care may not only reflect the effect of intervention strategies such as patient education, effective communication to the patient of the individual patients' level of asthma control and the possibility of improvement, written asthma management and action plans, but also the fact that a diagnosis of asthma was confirmed as an eligibility criterion, that the participants had poorly controlled disease, and that the possibility that their current treatment and their adherence to it were inadequate were both addressed [21]. It is quite possible that greater clinical improvement would have been observed in other trials that reported clinical outcomes had those samples consisted of patients with poorly controlled disease and had the nature of the regimen, as well as adherence, been addressed.

Effective Adherence Improvement Strategies in Vulnerable Populations

Hu et al. identified 36 studies of medication adherence interventions in various chronic diseases that were tested in exclusively or predominantly (≥75 %) African-American and Hispanic populations with chronic diseases; 20 studies obtained positive results for medication adherence [106]. However, a substantial proportion of the studies did not use any objective measure of adherence and relied upon self/caregiver report, including two of the four asthma studies [122, 123] and one of the three tuberculosis studies [124]. Among the conclusions of this review was that "Interventions demonstrating mixed results included motivational interviewing, reminder devices, community health worker (CHW) delivered interventions, and pharmacist-delivered interventions. DOT was a successful intervention in two studies. Interventions which did not involve human contact with patients were ineffective," and "No single intervention has been seen to be universally successful, particularly for patients from ethnic minority backgrounds" [106].

One of the key questions of the AHRQ-sponsored review also concerned the evidence for effective interventions in vulnerable populations, at risk for disparities in health care and health outcomes, especially those for whom English is a second language, those with low literacy, and those with low income and/or no or inadequate health insurance. The review found that African-Americans were well represented in the evidence base but that evidence was lacking for other minority groups. They concluded "that the evidence base for mainstream patient populations with common chronic conditions points toward a variety of medication adherence programs suitable for these (vulnerable) groups" [23]. No evidence has emerged suggesting that entirely different strategies are required in low-income or minority populations; however, translation as well as attention to an appropriate literacy level and cultural tailoring may be important in some populations.

Case or care management is a strategy that is typically adopted as a result of the high costs to the health care system of acute, emergency, and inpatient care for patients with poorly controlled chronic diseases, among which minority and low-income individuals are disproportionately represented. One large health care system in the southeastern US, whose patient population consists primarily of very low-income African-Americans and Spanish-speaking Hispanics, is implementing a shared decision-making care management intervention, based on the shared decision-making program developed and evaluated by Wilson et al. [21], which was updated, adapted to their setting, resources, and patients' reading level, modified for use with pediatric as well as adult asthma patients, and made available in both English and Spanish. The reception of this program by clinicians and patients at the first six clinics has been reported to be very positive, and the program is being extended to the more than 90 clinics of the health care system in a study of two implementation strategies [125, 126]. Some systematic reviews have referred to such intervention approaches as "complex," which may carry an unjustified implication that they are inherently only suitable for implementation in specific, especially well-resourced settings or with more educated or affluent patient populations. While they may be more likely to be used in larger health care settings that utilize population chronic disease management strategies and models, their modest cost and the initial effort to integrate them into ongoing clinical processes may prove to be fully justified by the results.

The possibility, discussed earlier, that the patient's regimen is inadequate has special salience when considering adherence intervention with patients from vulnerable demographic groups. Such patients have a disproportionately high likelihood of having poorly controlled disease. There is a compelling need to concurrently address both the treatment regimen and adherence in these and all patients with poorly controlled disease in order to bring about clinical improvement, especially of a magnitude that might be effective in reducing disparities in clinical outcomes. While this may seem obvious, to date it has not been typical in adherence intervention studies in respiratory disease to consider whether the patient's disease is poorly controlled (i.e., whether there is a clinical indication that their poor adherence is problematic), or the appropriateness of the regimen to which the patient is being asked to adhere. Further, the reviews to date, including of studies carried out in

vulnerable populations, have not considered either the appropriateness of the study target population or the possibility of an inadequate treatment regimen as a potential explanation of the lack of success of some trials.

Directions for Future Research

Additional research is clearly needed to understand the extent of disparities in medication adherence in respiratory disease and to determine the extent to which poor adherence and/or adherence disparities contribute to disparities in health outcomes. While the evidence of disparities in adherence is not as strong as the evidence of disparities in outcomes in respiratory diseases, given the significantly poorer outcomes seen in low-income minority populations and the central role of adherence in achieving positive outcomes, poor adherence, even if not disproportionate, is most likely a significant contributor to outcome disparities. To discern the extent to which outcome disparities are specifically attributable to nonadherence, it will be important to concurrently consider the adequacy of the patients' treatment regimens.

There is a further need to replicate and extend promising adherence improvement interventions in respiratory diseases and to determine whether these interventions work as well in low-income and minority populations as in more advantaged populations, and in both pediatric and adult patients. Well-designed trials of adherence interventions in vulnerable respiratory disease populations are limited, as are comparative analyses of subgroups of patients from adherence intervention studies that have significant numbers of minority and low-income participants. While some approaches are promising, more rigorous research is needed in order to determine whether such interventions can help reduce disparities in health outcomes in respiratory disease. Most research to date also has focused on asthma and tuberculosis, with some research in COPD, and there is a need for further studies to assess the effectiveness of such interventions in these and many other chronic lung diseases. A lack of detailed documentation of intervention procedures and materials also can be an obstacle to replication. In asthma, for example, we could identify only two studies that mentioned the availability of such materials [21, 115].

When carrying out adherence improvement studies, especially in vulnerable populations, it will be especially important to focus on the appropriate target—patients with poorly controlled chronic disease, and to use eligibility criteria appropriate to that purpose. It will also be important to ensure the quality of such research by adhering to current standards for clinical trials, especially with regard to reporting preplanned sample size determinations, and confirmation of the relevant diagnosis by objective evaluation.

Further, and especially when targeting adherence interventions to vulnerable patients who are at risk from poor health outcomes, it is essential to recognize that the existing regimen for many patients with poorly controlled disease may not adhere to current treatment guidelines. Many reviews have pointed out that the evaluation of adherence improvement interventions should include clinical outcomes as

well. However, attempting to motivate patients to follow an inadequate treatment regimen is both inappropriate and unlikely to be successful in improving outcomes. Clinical outcomes are affected by adherence and by what is being adhered to—the treatment regimen. Studies of the effectiveness of adherence interventions in vulnerable populations, as well as studies that compare intervention effects in vulnerable and mainstream populations, should characterize the regimens of study participants and should potentially simultaneously address both the regimen and medication adherence.

Adherence improvement intervention research, in general, will also benefit from greater standardization of adherence measures. Progressive advances have been made in the standardization of asthma outcome measures [127], but medication adherence measures have not been subjected to such standardization efforts. Agreement on a single adherence measure that suits all research and clinical purposes appears unlikely (if not impossible) when it comes to medications used to treat respiratory diseases, since they are administered by diverse routes and devices. However, it may be possible to achieve a closer consensus on objective measures within each of two basic classes, which might be used concurrently or alternatively, depending on the disease and study purpose: (1) indirect measures, based on pharmacy dispensing or refill data, of (a) adherence and (b) aggregate regimen potency, and (2) direct measures of adherence to (a) inhaled medications and (b) oral medications. Study of the relationships between the direct and indirect measures would also be important.

References

1. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. Am J Respir Crit Care Med. 1994;149(2):S69–76. doi:10.1164/ajrccm/149.2_Pt_2.S69.
2. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(3):371–84.
3. Newman S. Improving inhaler technique, adherence to therapy and the precision of dosing: major challenges for pulmonary drug delivery. Expert Opin Drug Deliv. 2014;11(3):365–78. doi:10.1517/17425247.2014.873402.
4. Sumino K, Cabana MD. Medication adherence in asthma patients. Curr Opin Pulm Med. 2013;19(1):49–53. doi:10.1097/MCP.0b013e32835b117a.
5. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2007;17(4), CD003343.
6. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. BMC Med Res Methodol. 2011;11:149. doi:10.1186/1471-2288-11-149.
7. Krishnan JA, Bender BG, Wamboldt FS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. J Allergy Clin Immunol. 2012;129(1):112–8. doi:10.1016/j.jaci.2011.10.030.
8. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. Respirology. 2008;13(4):559–63. doi:10.1111/j.1440-1843.2008.01292.x.

9. Bender B, Wamboldt FS, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. Ann Allergy Asthma Immunol. 2000;85(5):416–21.
10. Van Steenis M, Driesenaar J, Bensing J, et al. Relationship between medication beliefs, self-reported and refill adherence, and symptoms in patients with asthma using inhaled corticosteroids. Patient Prefer Adherence. 2014;8:83–91. doi:10.2147/PPA.S44185.
11. Reznik M, Ozuah PO. Measurement of inhaled corticosteroid adherence in inner-city, minority children with persistent asthma by parental report and integrated dose counter. J Allergy. 2012;2012:570850. doi:10.1155/2012/570850.
12. Fialko L, Garety PA, Kuipers E, et al. A large-scale validation study of the Medication Adherence Rating Scale (MARS). Schizophr Res. 2008;100(1–3):53–9. doi:10.1016/j.schres.2007.10.029.
13. Steele DJ, Jackson TC, Gutmann MC. Have you been taking your pills? The adherence-monitoring sequence in the medical interview. J Fam Pract. 1990;30(3):294–9.
14. Davis MS. Variations in patients' compliance with doctors' orders: analysis of congruence between survey responses and results of empirical investigations. J Med Educ. 1966;41(11):1037–48.
15. Finney JW, Hook RJ, Friman PC, Rapoff MA, Christophersen ER. The overestimation of adherence to pediatric medical regimens. Child Health Care. 1993;22(4):297–304. doi:10.1207/s15326888chc2204_5.
16. Ingerski LM, Hente EA, Modi AC, Hommel KA. Electronic measurement of medication adherence in pediatric chronic illness: a review of measures. J Pediatr. 2011;159(4):528–34. doi:10.1016/j.jpeds.2011.05.018.
17. Rudd P, Byyny RL, Zachary V, et al. The natural history of medication compliance in a drug trial: limitations of pill counts. Clin Pharmacol Ther. 1989;46(2):169–76.
18. Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. Curr Allergy Asthma Rep. 2011;11(6):454–64. doi:10.1007/s11882-011-0227-2.
19. Steiner JF, Koepsell TD, Fihn SD, Inui TS. A general method of compliance assessment using centralized pharmacy records. Description and validation. Med Care. 1988;26(8):814–23.
20. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol. 1997;50(1):105–16.
21. Wilson SR, Strub P, Buist AS, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med. 2010;181(6):566–77. doi:10.1164/rccm.200906-0907OC.
22. DiMatteo M. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200–9.
23. Viswanathan M, Golin C, Jones C. Medication adherence interventions: comparative effectiveness. 2012. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1248&pageaction=displayproduct. Accessed 9 Feb 2014.
24. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. J Asthma. 2010;47(2):162–5. doi:10.3109/02770900903497204.
25. Jones C, Santanello NC, Boccuzzi SJ, Wogen J, Strub P, Nelsen LM. Adherence to prescribed treatment for asthma: evidence from pharmacy benefits data. 2003. http://informahealthcare.com/doi/abs/10.1081/JAS-120017212. Accessed 7 Feb 2014.
26. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. Lancet. 1995;345(8964):1545–8. doi:10.1016/S0140-6736(95)91090-5.
27. Burrell C, Levy R. Therapeutic consequences of noncompliance. In: Improving medication compliance. Proceedings of a Symposium. Washington DC; 1984:7–16.
28. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. Am J Health Syst Pharm. 2003;60(7):657–65.
29. Noncompliance with medication regimens. An economic tragedy. In: Emerging issues in pharmaceutical cost containing. Washington DC: National Pharmaceutical Council; 1992:1–16.
30. Lindsay JT, Heaney LG. Nonadherence in difficult asthma—facts, myths, and a time to act. Patient Prefer Adherence. 2013;7:329–36. doi:10.2147/PPA.S38208.

31. Birkhead G, Attaway NJ, Strunk RC, Townsend MC, Teutsch S. Investigation of a cluster of deaths of adolescents from asthma: evidence implicating inadequate treatment and poor patient adherence with medications. J Allergy Clin Immunol. 1989;84(4):484–91.
32. National Center for Health Statistics. National hospital ambulatory medical care survey: 2010 emergency department summary Tables. 2010. http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2010_ed_web_tables.pdf. Accessed 27 Feb 2014
33. Bender BG, Rand C. Medication non-adherence and asthma treatment cost. Curr Opin Allergy Clin Immunol. 2004;4(3):191–5.
34. Iskedjian M, Addis A, Einarson T. Estimating the economic burden of hospitalization due to patient nonadherence in Canada. Value Health. 2002;5:420.
35. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy. 2014;7:35–44. doi:10.2147/RMHP.S19801.
36. Simmons MS, Nides MA, Rand CS, Wise RA, Tashkin DP. Trends in compliance with bronchodilator inhaler use between follow-up visits in a clinical trial. Chest. 1996;109(4):963–8. doi:10.1378/chest.109.4.963.
37. Sabaté E, World Health Organization. Adherence to long-term therapies evidence for action. Geneva: World Health Organization; 2003. http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=114059. Accessed 14 Feb 2014.
38. Oraka E, Iqbal S, Flanders WD, Brinker K, Garbe P. Racial and ethnic disparities in current asthma and emergency department visits: findings from the National Health Interview Survey, 2001–2010. J Asthma. 2013;50(5):488–96. doi:10.3109/02770903.2013.790417.
39. Shields AE, Comstock C, Weiss KB. Variations in asthma care by race/ethnicity among children enrolled in a state Medicaid program. Pediatrics. 2004;113(3):496–504.
40. Diette G, Wu A, Skinner E, et al. Treatment patterns among adult patients with asthma: factors associated with overuse of inhaled β-agonists and underuse of inhaled corticosteroids. Arch Intern Med. 1999;159(22):2697–704. doi:10.1001/archinte.159.22.2697.
41. Mansour ME, Lanphear BP, DeWitt TG. Barriers to asthma care in urban children: parent perspectives. Pediatrics. 2000;106(3):512–9. doi:10.1542/peds.106.3.512.
42. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids: socioeconomic and health-belief differences. Am J Respir Crit Care Med. 1998;157(6):1810–7. doi:10.1164/ajrccm.157.6.9712007.
43. Wijga AH, Zuidgeest MGP, Kerkhof M, Koppelman GH, Smit HA, de Jongste JC. Guideline-recommended use of asthma medication by children is associated with parental information and knowledge: the PIAMA birth cohort. Pharmacoepidemiol Drug Saf. 2014;23(4):406–10. doi:10.1002/pds.3584.
44. Diette GB, Rand C. The contributing role of health-care communication to health disparities for minority patients with asthma. Chest. 2007;132(5 suppl):802S–9. doi:10.1378/chest.07-1909.
45. Agh T, Inotai A, Meszaros A. Factors associated with medication adherence in patients with chronic obstructive pulmonary disease. Respiration. 2011;82(4):328–34. doi:10.1159/000324453.
46. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clin Med Res. 2013;11(2):54–65. doi:10.3121/cmr.2013.1113.
47. Dolce JJ, Crisp C, Manzella B, Richards JM, Hardin JM, Bailey WC. Medication adherence patterns in chronic obstructive pulmonary disease. Chest. 1991;99(4):837–41. doi:10.1378/chest.99.4.837.
48. Education NA, Program P. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138.

49. Brocklebank D, Ram F, Wright J, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess. 2001;5(26):1–149.
50. Van Beerendonk I, Mesters I, Mudde AN, Tan TD. Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered-dose inhaler or dry powder device. J Asthma. 1998;35(3):273–9. doi:10.3109/02770909809068218.
51. Rand C, Bilderback A, Schiller K, et al. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. J Allergy Clin Immunol. 2007;119(4):916–23. doi:10.1016/j.jaci.2006.12.664.
52. Sherman J, Patel P, Hutson A, Chesrown S, Hendeles L. Adherence to oral montelukast and inhaled fluticasone in children with persistent asthma. Pharmacotherapy. 2001;21(12):1464–7. doi:10.1592/phco.21.20.1464.34485.
53. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, Stanford RH, Ryskina KL, Legorreta AP. Adherence to asthma controller medication regimens. Respir Med. 2005;99(10):1263–7. doi:10.1016/j.rmed.2005.03.002.
54. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Rosenzweig C. R J. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. J Allergy Clin Immunol. 2004;113(2):245–51. doi:10.1016/j.jaci.2003.10.011.
55. Sovani MP, Whale CI, Oborne J, et al. Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help? Br J Gen Pract. 2008;58(546):37–43. doi:10.3399/bjgp08X263802.
56. Mann M, Eliasson O, Patel K, ZuWallack RL. A comparison of the effects of bid and qid dosing on compliance with inhaled flunisolide. Chest. 1992;101(2):496–9. doi:10.1378/chest.101.2.496.
57. Williams H, Jones ER, Sibert JR. Twice daily versus four times daily treatment with beclomethasone dipropionate in the control of mild childhood asthma. Thorax. 1986;41(8):602–5.
58. Coutts JA, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. Arch Dis Child. 1992;67(3):332–3.
59. Lobue P, Menzies D. Treatment of latent tuberculosis infection: an update. Respirology. 2010;15(4):603–22. doi:10.1111/j.1440-1843.2010.01751.x.
60. Lynd LD, Guh DP, Paré PD, Anis AH. Patterns of inhaled asthma medication use: a 3-year longitudinal analysis of prescription claims data from British Columbia, Canada. Chest. 2002;122(6):1973–81. doi:10.1378/chest.122.6.1973.
61. Foster JM, Smith L, Bosnic-Anticevich SZ, et al. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. Intern Med J. 2012;42(6):e136–44. doi:10.1111/j.1445-5994.2011.02541.x.
62. Ponieman D, Wisnivesky JP, Leventhal H, Musumeci-Szabó TJ, Halm EA. Impact of positive and negative beliefs about inhaled corticosteroids on adherence in inner-city asthmatic patients. Ann Allergy Asthma Immunol. 2009;103(1):38–42. doi:10.1016/S1081-1206(10)60141-X.
63. Armstrong ML, Duncan CL, Stokes JO, Pereira D. Association of caregiver health beliefs and parenting stress with medication adherence in preschoolers with asthma. J Asthma. 2014;51(4):366–72. doi:10.3109/02770903.2013.876431.
64. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf. 2006;5(2):231–49. doi:10.1517/14740338.5.2.231.
65. Chang SH, Eitzman SR, Nahid P, Finelli MLU. Factors associated with failure to complete isoniazid therapy for latent tuberculosis infection in children and adolescents. J Infect Public Health. 2013. doi:10.1016/j.jiph.2013.11.001.
66. Kwara A, Herold JS, Machan JT, Carter EJ. Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. Chest. 2008;133(4):862–8. doi:10.1378/chest.07-2024.

67. Sofianou A, Martynenko M, Wolf MS, et al. Asthma beliefs are associated with medication adherence in older asthmatics. J Gen Intern Med. 2013;28(1):67–73. doi:10.1007/s11606-012-2160-z.
68. Conn KM, Halterman JS, Lynch K, Cabana MD. The impact of parents' medication beliefs on asthma management. Pediatrics. 2007;120(3):e521–6. doi:10.1542/peds.2006-3023.
69. Menckeberg TT, Bouvy ML, Bracke M, et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. J Psychosom Res. 2008;64(1):47–54. doi:10.1016/j.jpsychores.2007.07.016.
70. Apter AJ, Boston RC, George M, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. J Allergy Clin Immunol. 2003;111(6):1219–26. doi:10.1067/mai.2003.1479.
71. McQuaid EL, Kopel SJ, Klein RB, Fritz GK. Medication adherence in pediatric asthma: reasoning, responsibility, and behavior. J Pediatr Psychol. 2003;28(5):323–33. doi:10.1093/jpepsy/jsg022.
72. Cooper W, Hickson G. Corticosteroid prescription filling for children covered by Medicaid following an emergency department visit or a hospitalization for asthma. Arch Pediatr Adolesc Med. 2001;155(10):1111–5. doi:10.1001/archpedi.155.10.1111.
73. Mosnaim G, Li H, Martin M, et al. Factors associated with levels of adherence to inhaled corticosteroids in minority adolescents with asthma. Ann Allergy Asthma Immunol. 2014;112(2):116–20. doi:10.1016/j.anai.2013.11.021.
74. McQuaid EL, Penza-Clyve SM, Nassau JH, et al. The asthma responsibility questionnaire: patterns of family responsibility for asthma management. Child Health Care. 2001;30(3):183–99.
75. Burgess S, Sly P, Devadason S. Adherence with preventive medication in childhood asthma. Pulm Med. 2011;2011:973849. doi:10.1155/2011/973849.
76. Walders N, Drotar D, Kercsmar C. The allocation of family responsibility for asthma management tasks in African-American adolescents. J Asthma. 2000;37(1):89–99.
77. Barr R, Somers SC, Speizer FE, Camargo Jr CA. Patient factors and medication guideline adherence among older women with asthma. Arch Intern Med. 2002;162(15):1761–8. doi:10.1001/archinte.162.15.1761.
78. Sestini P, Cappiello V, Aliani M, et al. Prescription bias and factors associated with improper use of inhalers. J Aerosol Med. 2006;19(2):127–36. doi:10.1089/jam.2006.19.127.
79. Gillman A, Douglass JA. Asthma in the elderly. Asia Pac Allergy. 2012;2(2):101–8. doi:10.5415/apallergy.2012.2.2.101.
80. Goeman DP, Douglass JA. Understanding asthma in older Australians: a qualitative approach. Med J Aust. 2005;183(1 Suppl):S26–7.
81. Enright PL. The diagnosis and management of asthma is much tougher in older patients. Curr Opin Allergy Clin Immunol. 2002;2(3):175–81.
82. Krishnan JA, Diette GB, Skinner EA, Clark BD, Steinwachs D, Wu AW. Race and sex differences in consistency of care with national asthma guidelines in managed care organizations. Arch Intern Med. 2001;161(13):1660–8. doi:10.1001/archinte.161.13.1660.
83. Irvine L, Crombie IK, Alder EM, Neville RG, Clark RA. What predicts poor collection of medication among children with asthma? A case-control study. Eur Respir J. 2002;20(6):1464–9. doi:10.1183/09031936.02.00302102.
84. Ho J, Bender BG, Gavin LA, O'Connor SL, Wamboldt MZ, Wamboldt FS. Relations among asthma knowledge, treatment adherence, and outcome. J Allergy Clin Immunol. 2003;111(3):498–502. doi:10.1067/mai.2003.160.
85. Tettersell MJ. Asthma patients' knowledge in relation to compliance with drug therapy. J Adv Nurs. 1993;18(1):103–13. doi:10.1046/j.1365-2648.1993.18010103.x.
86. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med. 2011;155(2):97–107. doi:10.7326/0003-4819-155-2-201107190-00005.

87. DeWalt DA, Berkman ND, Sheridan S, Lohr KN, Pignone MP. Literacy and health outcomes. J Gen Intern Med. 2004;19(12):1228–39. doi:10.1111/j.1525-1497.2004.40153.x.
88. Apter AJ, Wan F, Reisine S, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. J Allergy Clin Immunol. 2013;132(2):321–7. doi:10.1016/j.jaci.2013.02.014.
89. Christiaanse ME, Lavigne JV, Lerner CV. Psychosocial aspects of compliance in children and adolescents with asthma. J Dev Behav Pediatr. 1989;10(2):75–80.
90. Castaldi PJ, Rogers WH, Safran DG, Wilson IB. Inhaler costs and medication nonadherence among seniors with chronic pulmonary disease. Chest. 2010;138(3):614–20. doi:10.1378/chest.09-3031.
91. Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes. Pharm Ther. 2012;37(1):45–55.
92. Krauskopf KA, Sofianou A, Goel MS, et al. Depressive symptoms, low adherence, and poor asthma outcomes in the elderly. J Asthma. 2013;50(3):260–6. doi:10.3109/02770903.2012.757779.
93. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use and mortality in the United States, 2001–2010. Hyattsville, MD: National Center for Health Statistics; 2012.
94. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance—United States, 1971–2000. MMWR Surveill Summ. 2002;51(6):1–16.
95. Bosworth HB, Dudley T, Olsen MK, et al. Racial differences in blood pressure control: potential explanatory factors. Am J Med. 2006;119(1):70.e9–15. 10.1016/j.amjmed.2005.08.019.
96. Zhang Z, Peluso MJ, Gross CP, Viscoli CM, Kernan WN. Adherence reporting in randomized controlled trials. Clin Trials. 2014;11(2):195–204. doi:10.1177/1740774513512565.
97. Wells K, Pladevall M, Peterson EL, et al. Race-ethnic differences in factors associated with inhaled steroid adherence among adults with asthma. Am J Respir Crit Care Med. 2008;178(12):1194–201. doi:10.1164/rccm.200808-1233OC.
98. Williams LK, Joseph CL, Peterson EL, et al. Race-ethnicity, crime, and other factors associated with adherence to inhaled corticosteroids. J Allergy Clin Immunol. 2007;119(1):168–75. doi:10.1016/j.jaci.2006.09.029.
99. Gerber BS, Cho YI, Arozullah AM, Lee S-YD. Racial differences in medication adherence: a cross-sectional study of Medicare enrollees. Am J Geriatr Pharmacother. 2010;8(2):136–45. doi:10.1016/j.amjopharm.2010.03.002.
100. Wu AC, Smith L, Bokhour B, Hohman KH, Lieu TA. Racial/ethnic variation in parent perceptions of asthma. Ambul Pediatr. 2008;8(2):89–97. doi:10.1016/j.ambp.2007.10.007.
101. Le TT, Bilderback A, Bender B, et al. Do asthma medication beliefs mediate the relationship between minority status and adherence to therapy? J Asthma. 2008;45(1):33–7. doi:10.1080/02770900701815552.
102. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. Immunol Allergy Clin North Am. 2005;25(1):107–30. doi:10.1016/j.iac.2004.09.005.
103. Haynes RB, Wang E, Da Mota GM. A critical review of interventions to improve compliance with prescribed medications. Patient Educ Couns. 1987;10(2):155–66. doi:10.1016/0738-3991(87)90095-4.
104. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa R, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;11. Art. No.: CD000011. doi: 10.1002/14651858.CD000011.pub4.
105. Dunbar-Jacob J, Erlen J, Schlenk E, Ryan C, Sereika S, Doswel W. Adherence in chronic disease. Annu Rev Nurs Res. 2000;18:48–90.

106. Hu D, Juarez DT, Yeboah M, Castillo TP. Interventions to increase medication adherence in African-American and Latino populations: a literature review. Hawaii J Med Public Health. 2014;73(1):11.
107. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care. 1998;36(8):1138–61.
108. Tran N, Coffman JM, Sumino K, Cabana MD. Patient reminder systems and asthma medication adherence: a systematic review. J Asthma. 2014;51(5):536–43. doi:10.3109/02770903.2014.888572.
109. Charles MS, Blanchette CM, Silver H, Lavallee D, Dalal AA, Mapel D. Adherence to controller therapy for chronic obstructive pulmonary disease: a review. Curr Med Res Opin. 2010;26(10):2421–9. doi:10.1185/03007995.2010.516284.
110. Bryant J, McDonald VM, Boyes A, Sanson-Fisher R, Paul C, Melville J. Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. life. 2013;6:7. doi:10.1186/1465-9921-14-109.
111. DeFulio A, Silverman K. The use of incentives to reinforce medication adherence. Prev Med. 2012;55(Suppl):S86–94. doi:10.1016/j.ypmed.2012.04.017.
112. Glasscoe CA, Quittner AL. Psychological interventions for people with cystic fibrosis and their families. Cochrane Database Syst Rev. 2008;16(3), CD003148. doi:10.1002/14651858.CD003148.pub2.
113. Petry NM, Rash CJ, Byrne S, Ashraf S, White WB. Financial reinforcers for improving medication adherence: findings from a meta-analysis. Am J Med. 2012;125(9):888–96. doi:10.1016/j.amjmed.2012.01.003.
114. Bender BG, Apter A, Bogen DK, et al. Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. J Am Board Fam Med. 2010;23(2):159–65. doi:10.3122/jabfm.2010.02.090112.
115. Berg J, Dunbar-Jacob J, Sereika SM. An evaluation of a self-management program for adults with asthma. Clin Nurs Res. 1997;6(3):225–38. doi:10.1177/105477389700600304.
116. Janson SL, Fahy JV, Covington JK, Paul SM, Gold WM, Boushey HA. Effects of individual self-management education on clinical, biological, and adherence outcomes in asthma. Am J Med. 2003;115(8):620–6.
117. Janson SL, McGrath KW, Covington JK, Cheng S-C, Boushey HA. Individualized asthma self-management improves medication adherence and markers of asthma control. J Allergy Clin Immunol. 2009;123(4):840–6. doi:10.1016/j.jaci.2009.01.053.
118. Schaffer SD, Tian L. Promoting adherence: effects of theory-based asthma education. Clin Nurs Res. 2004;13(1):69–89. doi:10.1177/1054773803259300.
119. Williams LK, Peterson EL, Wells K, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. J Allergy Clin Immunol. 2010;126(2):225–31. doi:10.1016/j.jaci.2010.03.034. 231.e1-4.
120. Weinberger M, Murray MD, Marrero DG, et al. Effectiveness of pharmacist care for patients with reactive airways disease: a randomized controlled trial. JAMA. 2002;288(13):1594–602.
121. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. J Allergy Clin Immunol. 2012;129(3):S65–87. doi:10.1016/j.jaci.2011.12.986.
122. Joseph CLM, Peterson E, Havstad S, et al. A web-based, tailored asthma management program for urban African-American high school students. Am J Respir Crit Care Med. 2007;175(9):888–95. doi:10.1164/rccm.200608-1244OC.
123. Riekert KA, Borrelli B, Bilderback A, Rand CS. The development of a motivational interviewing intervention to promote medication adherence among inner-city, African-American adolescents with asthma. Patient Educ Couns. 2011;82(1):117–22. doi:10.1016/j.pec.2010.03.005.
124. Ailinger RL, Martyn D, Lasus H, Lima GN. The effect of a cultural intervention on adherence to latent tuberculosis infection therapy in Latino immigrants. Public Health Nurs. 2010;27(2):115–20. doi:10.1111/j.1525-1446.2010.00834.x.

125. Tapp H, Hebert L, Dulin M. Comparative effectiveness of asthma interventions within a practice based research network. BMC Health Serv Res. 2011;11:188. doi:10.1186/1472-6963-11-188.
126. Tapp H, Kuhn L, Alkhazraji T, et al. Adapting community based participatory research (CBPR) methods to the implementation of an asthma shared decision making intervention in ambulatory practices. J Asthma. 2014. doi:10.3109/02770903.2013.876430.
127. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. J Allergy Clin Immunol. 2012;129(3):S1–8. doi:10.1016/j.jaci.2011.12.985.

Chapter 7
Health Disparities in ARDS

Nancy Gonzalez Casanova, Jorge R. Navarrete, Hector Quijada, Louise Hecker, and Joe G.N. Garcia

Key Points

- Compared to other respiratory diseases, health disparities related to acute lung injury and acute respiratory distress syndrome outcomes have only recently been recognized and investigated.
- African Americans appear to be at increased risk of mortality due to acute lung injury.

The original version of this chapter was revised. An erratum to this chapter can be found at DOI 10.1007/978-3-319-23675-9_17

N.G. Casanova, M.D., M.P.H.
Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, 1656 E. Mabel St, Tucson, AZ 85724, USA

J.R. Navarrete, M.D.
Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, 1656 E. Mabel St. Room 412, Tucson, AZ 85724, USA
e-mail: jnavarrete@email.arizona.edu

H. Quijada, B.S.
Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, MRB 4th Floor, POB 245218, Tucson, AZ 85724, USA
e-mail: hquijada1@email.arizona.edu

L. Hecker, Ph.D.
University of Arizona, Southern Arizona VA Health Care System, Department of Medicine, 1656 E Mabel Street, Room 416, Tucson, AZ 85724, USA
e-mail: lhecker@email.arizona.edu
Supported by Veterans Administration Health System grant 1IK2BX001477 (L.H.)

J.G.N. Garcia, M.D. (✉)
Senior Vice President for Health Sciences, Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, Drachman Hall, 1295 N. Martin Ave, Tucson, AZ 85724, USA
e-mail: ncasanova@email.arizona.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_7

- Genetic variation may contribute to variability in acute lung injury outcomes by race and ethnicity, and several risk SNPs have been identified.
- Beyond genetic variation, other potential contributors to health disparities in acute lung injury outcomes include differences in risk related to factors that predispose to acute lung injury including sepsis, differences in the prevalence and severity of comorbid illness, and differences in health care quality and access to care.

Overview: Health Disparities and ARDS

In the context of health, the term "disparity" signifies not only a difference in health quality and access to care among groups, but it also denotes inequality and/or unfairness. Thus, "disparity" is inherently controversial and difficult to quantify. Multiple definitions of health disparities exist, and a variety of methods have been employed to measure these disparities. The National Healthcare Disparities Reports (NHDR) defines health disparity as "all differences among populations in measures of health and health care" and therefore assesses differences in group means. However, a limitation of this definition is that it does not account for health status and age differences between populations. The Institute of Medicine (IOM) defines health care disparities in the Unequal Treatment Report as "differences in health care services received by the two groups that are not due to differences in the underlying health care needs or preferences of the members groups." Under this definition, various factors are assessed in addition to differences in health status, such as differences due to the operation of health care systems, the legal and regulatory climate, and discrimination [1]. Health disparities are present when differences in health outcomes adversely affect groups of people who have experienced greater obstacles to health on the basis of factors including race, ethnicity, gender, age, and/or geographic location, such as rural and border areas. The adverse impact of health disparities extends to a much broader, societal level due to the resulting economic consequences, including the rising cost of health care and lost work-related efficiency and productivity.

Minority populations, including Hispanics and African Americans, are more frequently affected by these inequities, and these populations experience greater mortality from common complex health disorders than non-Hispanic whites. In general, minorities receive less and poorer quality health care. The combined direct and indirect cost of health disparities for minorities in the USA between 2003 and 2006 was estimated at $1.23 trillion; direct medical expenditures were estimated at $230 billion and indirect costs associated with illness and premature death were approximately $1 trillion [2]. Eliminating health inequalities for minorities would greatly reduce indirect costs on society, impacting worker productivity and losses from premature death. The U.S. Department of Health and Human Services has acknowledged the importance of addressing social determinants of health through the Healthy People program, which provides science-based 10-year objectives for improving the health of Americans; a major goal outlined for 2020 is to eliminate disparities and improve the health of all groups (www.healthypeople.gov).

Because racial and ethnic identity are not only related to genetic ancestry but are also inextricably linked to socioeconomic status, cultural/historical heritage, and access to health care, the study of health disparities in racial/ethnic minority groups poses many challenges, and this is particularly true for health disparities research related to critical illness. In comparison to other respiratory diseases, health disparities in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have only recently begun to be described and investigated. In the USA, racial/ethnic minorities suffer disproportionately from preventable and treatable conditions including ALI and ARDS among the critically ill [3, 4]. ARDS is a heterogeneous critical illness with mortality often exceeding 30–40 % [5, 6]. ARDS is characterized by acute diffuse inflammatory lung injury, increased vascular permeability, and flooding of alveoli with protein-rich fluid, resulting in devastating physiologic derangements that cause acute respiratory failure. Under the Berlin definition, ALI and ARDS are defined by acute onset bilateral infiltrates on chest imaging associated with hypoxemia determined by a reduced ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) in the absence of left atrial hypertension. ARDS severity is based on the degree of hypoxemia: mild (PaO_2/FiO_2 200–300), moderate (PaO_2/FiO_2 100–200), and severe ($PaO_2/FiO_2 < 100$), and each category has a mortality index. Compared with the previous AECC definition, the current Berlin definition is better at predicting mortality [7]. Recent epidemiologic studies indicate that minority populations demonstrate increased risk for ARDS and associated mortality [8–10]. This chapter will review various factors that may contribute to this important and devastating disparity.

Health Disparities in ARDS Risk and Outcomes

Epidemiologic studies have demonstrated differences in ARDS incidence and mortality by race/ethnicity. Moss and Mannino (2002) reported that the annual ARDS mortality rates in the USA were higher for African American patients when compared with whites during 1979–1996. Further, African American men had the highest annual age-adjusted mortality rate from ARDS, compared with other race/ethnicity and gender subgroups [8]. This raised the question of whether the increased mortality among African Americans was associated with higher risk of diagnoses leading to ARDS, such as pneumonia, sepsis, or trauma; whether race/ethnicity may influence the care of these patients with ARDS; and/or whether socioeconomic status and access to care may contribute to these outcomes. A recent multicenter observational cohort study of 5201 patients at risk for ALI showed no significant difference in in-hospital ALI-related mortality by race or sex after adjusting for potential confounders [11]. However, it demonstrated differences in clinical presentation based on race; African Americans more frequently presented with ARDS in the setting of pneumonia, sepsis, or shock and had higher severity of illness [11]. While African Americans were more likely to present with greater severity of illness in this study, they were overall less likely to develop ALI compared to white patients (4.5 % vs. 6.5 %, $p = 0.014$). This study's findings are in contrast to prior

work published by investigators from the ARDS Network which reported that African American and Hispanic patients are at significantly higher risk of death from ARDS compared to white patients [9]. In summary, the limited available evidence suggests that African Americans are at higher risk of ARDS-related mortality but may be at lower risk of developing ARDS, and likewise Hispanics appear to be at higher risk of death due to ARDS.

Factors Influencing Health Disparities in ARDS

Differences in the quality and intensity of care by race may influence racial differences in ARDS-related outcomes. For example, differences also exist in the intensity of ICU care at the end of life in non-white patients compared with white patients [12]. Similarly in one study black patients with pneumonia were less likely to receive antibiotics within the recommended 4-h window than white patients, even after adjusting for severity of illness and other patient factors [13]. Hospital characteristics are other contributors that may be correlated to outcome disparities. For instance, minorities with severe sepsis are more likely to be treated in larger urban academic centers, and differences in care variation across hospitals have been demonstrated [14, 15].

As noted throughout this book, racial and ethnic minorities experience higher levels of poverty. Income is linked with health regardless of racial or ethnic group, but differences in health status by income do not completely capture the differences by race or ethnicity [16]. Minorities of low SES are more susceptible to experiencing diminished quality of life and increased burden of respiratory disease, as they are up to 14 times more likely to have respiratory diseases as compared to higher SES social groups [17]. Likewise environmental exposure and occupational hazards are more common among the lowest socioeconomic groups as well, with the lungs being the most immediate organ affected by environmental exposures such as tobacco smoke, air pollution, and occupational inhalants. Multidisciplinary strategies such as reducing environmental exposures, promoting a healthy life style, and improving the quality of health care are likely needed to significantly ameliorate these disparities. However, the role that these individual factors play in the development of ARDS remains largely unexplored, cultural competence at all levels of care has been recommended as a strategy to address disparities, based on the premise that improving provider-patient communication is an important component of addressing differences in quality of care that are based on the race, ethnicity, or culture of the patient [18]. Cultural competence enables providers to deliver services that are respectful of and responsive to the health beliefs, practices, and cultural and linguistic needs of diverse patients and favors treatment adherence. A cross-sectional analysis of the multi-center, randomized trials conducted by the ARDS Network from 1996 to 2005 failed to find significant evidence of sex or racial/ethnic minorities underrepresentation in ARDS clinical trials [19, 20], although it should be noted that this study also reported that Black, Hispanic, and American/Indian/Alaskan Native patients were more often

Table 7.1 Most common conditions associated with ARDS by race

Race	Condition	Reference
African Americans	Sepsis, pneumonia	[11, 14, 24]
Asians	Aspiration, trauma	[10, 11]
Hispanics	Sepsis, trauma	[9, 11]
Whites	Surgery	[9, 11]

unable to be consented for research participation due to the lack of surrogate or family refusal. This may reflect existing mistrust of the research environment, lack of research staff diversity, and/or language and communication barriers [19]. Although the majority of studies on disparities in critical care illnesses have focused primarily on race differences, Hispanic patients have not been sufficiently represented in prior studies [6].

Predisposing Conditions and ARDS

While ARDS is associated with preexistent conditions such as sepsis, trauma, gastric acid aspiration, excessive mechanical ventilation and pneumonia [21–23], only a fraction of patients exposed to ARD-Sinciting events actually develop the syndrome. Epidemiologic studies over the past several decades have shown that race and gender influence sepsis-related deaths, and sepsis is a major risk factor for ARDS. Prior work has suggested that at least one possible reason for racial differences in ARDS mortality may be due to the fact that African Americans are thought to be at higher risk of severe sepsis [8]. Severe sepsis, defined by international consensus conference criteria, includes an infection plus acute organ dysfunction, and it represents a considerable public health burden that afflicts over 750,000 Americans each year. Sepsis was the most at-risk common condition associated with non-cardiogenic acute respiratory failure across racial and ethnic groups according to the National Hospital Discharge Survey (NHDS) database (1992–2007) [24]. African Americans have an increased risk for sepsis and other high-risk conditions that predispose them to develop acute respiratory failure. This increased susceptibility may be multifactorial, including higher proportion of chronic conditions over extended time and environmental, socioeconomic, and genetic factors. Table 7.1 shows the most common predisposing conditions associated with ARDS by race category [9–11, 14, 24]. African Americans have the highest rate of severe sepsis, followed by Latinos then whites; this corresponds with a rate ratio (RR) of 1.7 for blacks and 1.1 for Latinos, compared to whites [25]. Moreover, blacks had the highest sepsis-related mortality compared to other races when adjusting for age and sex, followed by Hispanics and whites ($p < 0.0001$). In complicated cases of severe sepsis requiring ICU admission, blacks with severe sepsis were more likely to die if they were admitted to the ICU ($p < 0.0001$) [14].

According to data from a National Trauma Data Bank study, there was no evidence to support significant differences in ARDS incidence, severity, or mortality based on race in trauma patients [10]. Interestingly, in a previous study, Black and

Table 7.2 Comorbidities associated with severe sepsis

Sepsis comorbidity	Non-Latino Black (%)	Latinos (%)	Non-Latinos White (%)
Diabetes	18.7	19.7	15.1
Renal infection	35.3	30.2	32.7
Lung infection	38	38.6	42.6
ICU admission	54.3	52	53.6

Source: Adapted from Barnato, AE et al. [14]

Hispanic patients showed a significantly higher risk of death compared to whites, and this risk seemed to be associated with illness severity in blacks but not in Hispanics [9]. In addition, Hispanics were reported to have significantly fewer ventilator-free days compared to whites and African Americans [9]. Racial differences in predisposing comorbidities and outcomes have been documented as well. Mortality rate in ARDS is higher in African Americans and Hispanics than in other groups in the USA [8]. Likewise, the incidence of sepsis among black patients is proportionally higher compared to white patients [9, 14, 24]. The difference in the outcomes between subjects with sepsis associated with other comorbidities suggests that the presence of comorbidities may place patients at a higher mortality risk if ARDS is present (Table 7.2).

Genetic Susceptibility as a Contributor to ARDS Disparities

Given that African Americans and Latinos have increased risk of ALI mortality, significant interest exists for the identification of genetic and non-genetic factors potentially contributing to ARDS susceptibility and prognosis [26]. Individual genetic variation may be responsible for conferring differing risks with respect to ALI outcomes among different racial groups.

In the era of personalized medicine, study of the human genome is providing increasing insight into the role of race and ethnic variations in multiple complex disorders including the influence of single nucleotide polymorphisms (SNPs) on susceptibility and severity of sepsis and sepsis-associated ARDS [27–35]. Due to the increasing number of epidemiologic studies that implicate race may play a role in the large heterogeneity associated with ARDS outcomes, several strategies have been developed to identify race-specific candidate genes. Using a candidate gene-based case-control association study, sampling distinct individuals from the population of patients and controls was performed to assess differences in the frequency of variants in genes of interest. Candidate gene variants were identified by analyzing publicly known SNPs or via gene sequencing [36] and SNPs associated with human ARDS were determined, with unique variants observed specifically in African Americans. Highly differentially regulated genes between the apex and base regions included several genes commonly associated with ARDS: vascular endothelial growth factor (VEGF), thrombospondin 1 (THBS1), plasminogen activator inhibitor 1 (PAI-1),

transforming growth factor β (TGF-β), and pre-B cell colony-enhancing factor (PBEF) [37]. Several variants of genes involved in inflammatory and innate responses to infection showed different allelic frequencies by race and gender in ARDS and sepsis, suggesting that race and gender may have variable inherent response to infection [38]. Studies, however, suggest that genetic variation alone does not fully explain the differences in outcomes with respect to common acute critical illness. Immunologic and inflammatory diseases are associated with a large number of genetic markers with a large variance among different ethnic populations. Examples of this variation have been associated with individuals of African descent and individuals of non-African descent with either the presence of diseases associated with the inflammatory and/or infection pathways, or for which the susceptibility allele occurs at a larger frequency. Examples include the 237G allele of the beta chain of the high-affinity IgE receptor [FCER1B]; the -589T allele of interleukin (IL)-4 receptor alpha; the P46L (c.224C>T) variant in the gene encoding member 1A of tumor necrosis factor receptor superfamily (TNFRSF1A); the -174G/G genotype in the pro-inflammatory cytokine IL-6 gene; and the -401A allele of RANTES [35, 39]. Moreover, there are gene variants that have been associated with sepsis development and ARDS. For example, Saleh et al. identified CGA (Arg) codon resulting in a full-length caspase polypeptide (Csp12-L) associated with severe sepsis and a higher mortality due to sepsis; this variant confers hypo-responsiveness to LPS-stimulated cytokine production and is present in approximately 20 % of African descent but is absent in Europeans and Asians [40]. Tumor necrosis factor alpha has also been associated with ARDS. Similarly, the functional rs2814778 SNP in the gene encoding Duffy antigen/receptor for chemokines is associated with worse clinical outcomes among African Americans with ARDS, possibly via an increase in circulating IL-8 [41].

Candidate gene-based studies from our laboratory utilizing preclinical models of sepsis and ARDS identified a number of genes that have been shown to be associated with features of ARDS pathobiology [28, 30, 35, 36, 42, 43]. For example, two genes associated with ARDS susceptibility include NAMPT/PBEF (*NAMPT*) and myosin light chain kinase (*MYLK*). PBEF was identified from high-throughput expression profiling in animal models of ARDS and in human patients following ALI [35, 43]. PBEF protein levels were elevated in human bronchoalveolar lavage and serum samples from patients with ARDS, and also DNA sequencing identified two SNPs in the PBEF promoter that were overrepresented in patients with sepsis-induced ARDS [26]. Variants in the promoter region of PBEF were shown to confer a 7.7-fold higher risk of sepsis-associated ALI ($p < 0.001$) compared with both individuals with severe sepsis and healthy control subjects. Additionally, functional studies have further validated PBEF as a novel biomarker in ARDS [30, 39]. PBEF is not only an essential participant in ventilator-induced lung injury (VILI), but also a key regulator of cellular apoptosis and vascular barrier regulation.

MYLK is a multifunctional Ca^{2+}/calmodulin (CaM)-dependent kinase in endothelium that contributes to endothelial contraction and barrier dysfunction. The human MYLK encodes three proteins including non-muscle and smooth muscle myosin light chain involved in cell motility, vascular regulation of inflammation, permeability, and apoptosis [36, 42, 43], with an important role in endothelial/epithelial barrier dysfunction and vascular leak, trademarks of ARDS. Direct sequencing of *MYLK* in

individuals of European and African descent with sepsis, sepsis-associated ARDS, and healthy controls identified 57 genetic variations and 51 polymorphic base substitutions. Five of ten *MYLK* SNPs conferred an amino acid change and four novel polymorphisms. Genotyping studies showed several *MYLK* SNPs to be overrepresented in Caucasians as well as several SNPs overrepresented in African Americans. These observations implicate a variety of potential contributors that may influence ARDS incidence and mortality. Recent reports support a genetic/epigenetic predisposition to ARDS, with several studies highlighting individual genetic variation as a contributor to ALI susceptibility with increased frequency of ARDS-associated variants in individuals with African descent. For example, the coding SNPs in *MYLK*, rare in European descendants but frequent in those of African descent, confer susceptibility to ARDS as well as severe asthma in African Americans [36].

Chronic Comorbid Conditions Associated with ARDS Disparities

African American and Hispanic/Latino populations exhibit decreased life expectancy and disproportionately higher morbidity and mortality from preventable diseases [38, 44]. These include the burden of acute and chronic lung diseases, conditions well established to be significant and distributed unevenly across gender, ethnic, and social groups, including African Americans and Latinos [44]. A well-established Index of comorbidity, the Charlson Comorbidity Index (CCI), has been used to assess the comorbidities in ARDS patients. CCI has been statistically significantly correlated with the acute physiology and chronic health evaluation score, also known as APACHE II, and sequential organ failure assessment (SOFA) score ($r=0.387$, $p<0.01$ and $r=0.288$, $p<0.05$, respectively) [45]. The CCI score is determined through the sum of an already established point value for categories of comorbidities, where each condition category is scored from 1 to 6 (Table 7.1). Examination of the CCI list of comorbidities indicates there are several which are more common among racial and ethnic minorities. Chronic untreated conditions such as diabetes are more often seen in minorities and some of these conditions, such as diabetes, predispose to sepsis development [14]. African American septic patients are more likely to have diabetes, chronic renal failure, obesity, and HIV compared to whites (Table 7.3).

A retrospective cohort study analyzing 47 patients over 198.2 days (6.6 months) using CCI showed that the prognosis of ARDS was affected more by comorbidity than by age [45].

It has been estimated that the overall chronic disease prevalence will increase 42 % by 2023 and the projected economic burden will be about $4.2 trillion; that includes the economic cost associated with obesity, diabetes, and hypertension, conditions with higher prevalence among blacks and Hispanics [46]. Increasing access to interventions that enhance outcomes and care of individuals with chronic preexisting conditions may decrease ARDS incidence and improve its prognosis (Table 7.4).

Table 7.3 Charlson Comorbidity Index (CCI)

Points	Comorbidities
1	Dementia
	Peripheral vascular disease
	Myocardial infraction
	Congestive heart failure
	Ulcer disease
	Mild liver disease
	Diabetes (without complications)
	Chronic pulmonary disease
	Cerebrovascular disease
2	Lymphoma, multiple myeloma
	Leukemia
	Diabetes (with end organ damage)
	Hemiplegia
	Moderate or severe renal disease
	Second solid not metastatic tumor
3	Moderate or severe liver disease
6	Second solid metastatic tumor
	AIDS

Comorbidities commonly found in minorities are italicized

Table 7.4 Chronic disease: current and projected burden, USA, 2003–2023

Chronic disease	Increase in prevalence (%)	Current cost (billion $) (2003)	Future cost (billion $) (2023)
Overall chronic illness	42	271	814
Diabetes	53	132	430
Pulmonary conditions	31	139	384

Source: Adapted from Bodenheimer T et al. [46]

Access to Care Effect on Disparities

Despite substantial evidence documenting racial and ethnic disparities in health care, the analysis of the factors involved in these disparities continues to be a challenging and complex process. Health status is intrinsically related to several factors, including health services use, socioeconomic status, physical environment, discrimination, racism, and literacy levels. These factors are known to be associated with race and ethnicity; furthermore, Black and Latino patients live in geographically segregated regions and use different hospitals than whites [25, 47]. The complex relationships between health and biology, genetics, and individual behavior likely contribute to ARDS disparities.

In the USA, health care access is a significant determinant of health status; particularly due to the way the health system is organized. The presence or absence of health insurance defines individual access to medical care and consequently health condition throughout life. Data from the National Healthcare Quality Report (NHQR) 2013 indicates that 26 % of Americans reported barriers that restricted their access to care. In addition to issues with health care access, disparities also exist with regard to quality of care, with Blacks and Hispanic/Latinos receiving decreased quality of health care compared to non-Hispanic whites. Most of these disparities of care related to race, ethnicity, or income have remained without any significant change over the past several years [16]. Uninsured individuals are less likely to have a regular source of care, are more likely to report delaying seeking care, and are more likely to report that they have not received needed care—all resulting in experiencing avoidable hospitalizations, emergency hospital care, and adverse health outcomes [17].

Data from Healthy People 2020 shows that delays in accessing or inability to obtain necessary medical care is directly related to the Federal Poverty Level (FPL) with Blacks and Hispanics disproportionately affected [48]. African Americans and Hispanics had lower odds of receiving pneumococcal vaccination, smoking cessation counseling, first antibiotic dose within 4 h of accessing the emergency room, and influenza vaccination [49]. Pneumococcal immunization and influenza immunization among hospitalized patients with pneumonia and long-stay nursing home residents are some of the several quality measures for prevention of pneumonia, a condition that is frequently associated with ARDS [16]. Alcohol abuse, which is commonly found in African Americans, Hispanics, and Native Americans, is associated with higher acuity of acute critical illnesses, as well as higher rates of sepsis, pancreatitis, ARDS, and organ dysfunction.

Summary

Further ARDS research studies focused on Latinos are needed to improve the understanding of the ethnic differences and racial mixture present in minority groups. The American Thoracic Society (ATS) Executive Committee recognizes these disparities as one of the most important contributors to the health expenses in the health care system and has created a Health Equality Subcommittee with the purpose to direct efforts to eliminate respiratory health disparities. In order to address these inequities, efforts from multiple stakeholders, such as government, health care professionals, and other members of the society are required [49]. In addition, research efforts directed to better understand the genetic variation and environmental interaction among Latinos, African Americans, Native Americans, and other minorities are much needed in order to understand the multifactorial causes associated with disparities that predispose to critical illness and adverse outcomes. The health care system in the USA has entered into a transformation phase, with the Affordable Care Act offering the possibility to address the health care inequities and access among minorities thereby decreasing the impact of comorbid conditions that predispose and influence the course of critical care illnesses. In addition, the rapid growth in research focused on the genomic and epigenetic analysis of ARDS risk and outcomes in specific populations may allow integration with personalized medicine as part of routine medical care.

References

1. Cook BL, McGuire TG, Zaslavsky AM. Measuring racial/ethnic disparities in health care: methods and practical issues. Health Serv Res. 2012;47(3 Pt 2):1232–54.
2. LaVeist TA, Gaskin D, Richard P. Estimating the economic burden of racial health inequalities in the United States. Int J Health Serv. 2011;41(2):231–8.
3. Mathur R, et al. Cardiovascular multimorbidity: the effect of ethnicity on prevalence and risk factor management. Br J Gen Pract. 2011;61(586):e262–70.
4. DeVol R, Armen B. An unhealthy America: the economic burden of chronic disease. chronic_disease_report.pdf. Milken Institute; 2007. http://www.milkeninstitute.org/publications/view/321
5. Rubenfeld GD, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–93.
6. Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. Chest. 2008;133(5):1120–7.
7. Ranieri VM, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33.
8. Moss M, Mannino DM. Race and gender differences in acute respiratory distress syndrome deaths in the United States: an analysis of multiple-cause mortality data (1979–1996). Crit Care Med. 2002;30(8):1679–85.
9. Erickson SE, et al. Racial and ethnic disparities in mortality from acute lung injury. Crit Care Med. 2009;37(1):1–6.
10. Brown LM, et al. The influence of race on the development of acute lung injury in trauma patients. Am J Surg. 2011;201(4):486–91.
11. Lemos-Filho LB, et al. Sex, race, and the development of acute lung injury. Chest. 2013;143(4):901–9.
12. Muni S, et al. The influence of race/ethnicity and socioeconomic status on end-of-life care in the ICU. Chest. 2011;139(5):1025–33.
13. Mayr FB, et al. Do hospitals provide lower quality of care to black patients for pneumonia? Crit Care Med. 2010;38(3):759–65.
14. Barnato AE, et al. Racial variation in the incidence, care, and outcomes of severe sepsis: analysis of population, patient, and hospital characteristics. Am J Respir Crit Care Med. 2008;177(3):279–84.
15. Skinner J, et al. Mortality after acute myocardial infarction in hospitals that disproportionately treat black patients. Circulation. 2005;112(17):2634–41.
16. Agency for Healthcare Research and Quality. National Healthcare QualityReport 2013. Rockville: AHRQ; 2013(14-0005).
17. Andrulis DP. Access to care is the centerpiece in the elimination of socioeconomic disparities in health. Ann Intern Med. 1998;129(5):412–6.
18. Betancourt JR, Corbett J, Bondaryk MR. Addressing disparities and achieving equity: cultural competence, ethics, and health-care transformation. Chest. 2014;145(1):143–8.
19. Cooke CR, Erickson SE, Watkins TR, Matthay MA, Hudson LD, Rubenfeld GD. Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials. Crit Care Med. 2010;38(6):1450–7.
20. Wiener RS. Examining disparities in Acute Respiratory Distress Network trial enrollment: moving closer to evidence-based medicine. Crit Care Med. 2010;38(6):1493–4.
21. Slutsky AS. Lung injury caused by mechanical ventilation. Chest. 1999;116(1 Suppl):9S–15.
22. Tremblay LN, et al. Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor-alpha and interleukin-6 messenger RNA. Crit Care Med. 2002;30(8):1693–700.
23. Kamat PP, et al. Mechanical ventilation exacerbates alveolar macrophage dysfunction in the lungsof ethanol-fed rats. Alcohol Clin Exp Res. 2005;29(8):1457–65.
24. Cooke CR, et al. Trends in the incidence of noncardiogenic acute respiratory failure: the role of race. Crit Care Med. 2012;40(5):1532–8.

25. Celedón JC, et al. Respiratory health equality in the United States. The American Thoracic Society perspective. Ann Am Thorac Soc. 2014;11(4):473–9.
26. Garcia JG. Genomic investigations into acute inflammatory lung injury. Proc Am Thorac Soc. 2011;8(2):167–72.
27. Prows DR, et al. Genetic susceptibility to nickel-induced acute lung injury. Chemosphere. 2003;51(10):1139–48.
28. Villar J, Flores C, Méndez-Alvarez S. Genetic susceptibility to acute lung injury. Crit Care Med. 2003;31(4 Suppl):S272–5.
29. Wesselkamper SC, et al. Genetic susceptibility to irritant-induced acute lung injury in mice. Am J Physiol Lung Cell Mol Physiol. 2000;279(3):L575–82.
30. Ye SQ, et al. Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med. 2005;171(4):361–70.
31. Gao L, et al. Novel polymorphisms in the myosin light chain kinase gene confer risk for acute lung injury. Am J Respir Cell Mol Biol. 2006;34(4):487–95.
32. Flores C, et al. A common haplotype of the LBP gene predisposes to severe sepsis. Crit Care Med. 2009;37(10):2759–66.
33. Wurfel MM, et al. Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. Am J Respir Crit Care Med. 2008;178(7):710–20.
34. Gao L, et al. Polymorphisms in the myosin light chain kinase gene that confer risk of severe sepsis are associated with a lower risk of asthma. J Allergy Clin Immunol. 2007;119(5):1111–8.
35. Flores C, et al. IL6 gene-wide haplotype is associated with susceptibility to acute lung injury. Transl Res. 2008;152(1):11–7.
36. Garcia JG, Moreno Vinasco L. Genomic insights into acute inflammatory lung injury. Am J Physiol Lung Cell Mol Physiol. 2006;291(6):L1113–7.
37. Meyer NJ, Garcia JG. Wading into the genomic pool to unravel acute lung injury genetics. Proc Am Thorac Soc. 2007;4(1):69–76.
38. Soto GJ, Martin GS, Gong MN. Healthcare disparities in critical illness. Crit Care Med. 2013;41(12):2784–93.
39. Barnes KC. Genetic determinants and ethnic disparities in sepsis-associated acute lung injury. Proc Am Thorac Soc. 2005;2(3):195–201.
40. Saleh M, et al. Enhanced bacterial clearance and sepsis resistance in caspase-12-deficient mice. Nature. 2006;440(7087):1064–8.
41. Kangelaris KN, et al. The association between a Darc gene polymorphism and clinical outcomes in African American patients with acute lung injury. Chest. 2012;141(5):1160–9.
42. Christie JD, et al. Variation in the myosin light chain kinase gene is associated with development of acute lung injury after major trauma. Crit Care Med. 2008;36(10):2794–800.
43. Garcia JG, et al. Myosin light chain kinase in endothelium: molecular cloning and regulation. Am J Respir Cell Mol Biol. 1997;16(5):489–94.
44. Garcia JG, Sznajder JI. Healthcare disparities in patients with acute respiratory distress syndrome. Toward equity. Am J Respir Crit Care Med. 2013;188(6):631–2.
45. Ando K, et al. The effect of comorbidity on the prognosis of acute lung injury and acute respiratory distress syndrome. Intern Med. 2012;51(14):1835–40.
46. Bodenheimer T, Chen E, Bennett HD. Confronting the growing burden of chronic disease: can the U.S. health care workforce do the job? Health Aff (Millwood). 2009;28(1):64–74.
47. Jha AK, et al. Concentration and quality of hospitals that care for elderly black patients. Arch Intern Med. 2007;167(11):1177–82.
48. Healtypeople.gov. Healthy People 2010. 2013. http://www.healthypeople.gov/2020/data/default.aspx.
49. Hausmann LR, et al. Racial and ethnic disparities in pneumonia treatment and mortality. Med Care. 2009;47(9):1009–17.

Chapter 8
Social Disparities in Lung Growth and Respiratory Health

Kelly J. Brunst and Rosalind J. Wright

Key Points

- The etiology of sociodemographic disparities in respiratory disease outcomes is not well understood.
- While a number of theoretical models explaining how social conditions get into the body to impact health are proposed, the psychosocial stress model has been increasingly adopted.
- Social toxicity experienced as increased psychological stress is a likely driver of observed disparities in lung growth and development and a range of other respiratory conditions.
- A life course framework that considers biological, psychological, and social processes interacting throughout the life course to influence disease expression is needed.
- Beginning in utero, stress influences programming of integrated physiological systems in offspring (e.g., neuroendocrine, autonomic, immune function, oxidative stress) that impacts lung growth and development and respiratory disease risk.
- Multiple mechanistic pathways with complex interdependencies must be considered when examining the integrative influence of stress independently as well as the interaction of social and physical environmental toxins in explaining the social patterning of respiratory diseases.

K.J. Brunst, Ph.D.
Department of Pediatrics, Kravis Children's Hospital at Mount Sinai, New York, NY, USA

R.J. Wright, MD., M.P.H. (✉)
Department of Pediatrics, Kravis Children's Hospital at Mount Sinai, New York, NY, USA

Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: rosalind.wright@channing.harvard.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_8

Introduction

It is well established that socioeconomic status (SES) influences health with SES disparities being observed across a range of health outcomes in adults including cardiovascular disease, diabetes, and mental health [1–3]. More recently, sociodemographic disparities in respiratory disease outcomes including lung function [4–6], wheezing [7], asthma [8–11], and chronic obstructive pulmonary disease (COPD) [12, 13] have been documented.

An area of particular interest is the search for mechanisms responsible for health disparities across economic and ethnic groups which may inform intervention and prevention strategies aimed at reducing such disparities. While a number of theoretical models explaining how social conditions "get into the body" to impact health more broadly have been proposed, the psychosocial stress model has been increasingly adopted in this regard [14, 15]. It has been suggested that much of the observed SES and racial disparities may be determined by increased exposure to acute and chronic stress, psychological correlates of stress (i.e., anxiety, depression), and lack of control over one's life [15, 16]. According to this framework, the likelihood of having reduced lung function and higher rates of respiratory disease and associated morbidity is greater among lower SES groups because they bear a disproportionate burden of exposure to suboptimal, socially toxic environments and experience increased social stress. However, in order to examine this hypothesis in epidemiological research, it is necessary to consider several key theoretic and methodological principles involving social sciences, psychology, immunology, and developmental biology and their interconnections as detailed herein. In order to exemplify these concepts, we focus our discussion on lung growth and development as well as a major determinant of chronic airway inflammation in early life—asthma—which impacts lung function trajectories over the life course (Fig. 8.1).

Early Life Programming of Lung Structure and Function

Exposure to negative social factors (e.g., low SES, psychological stress) during prenatal and/or early childhood development may alter the normal course of lung morphogenesis, resulting in changes that affect both structure and function of the respiratory system [17, 18]; this is referred to as developmental plasticity. The fetal and infant respiratory system may be particularly vulnerable, in part, due to the long developmental and maturation period of the lung [19]. Lung development starts in utero and progresses through a series of carefully orchestrated stages starting with establishment of core lung structure with airway branching in the embryonic (4–7 weeks gestation) and pseudoglandular (5–17 weeks) stages of early lung development. This is followed by the canalicular stage (16–24 weeks) during which air spaces are beginning to open with subsequent formation of saccular units in the airways during the saccular stage (24–35 weeks); secondary septa divide the

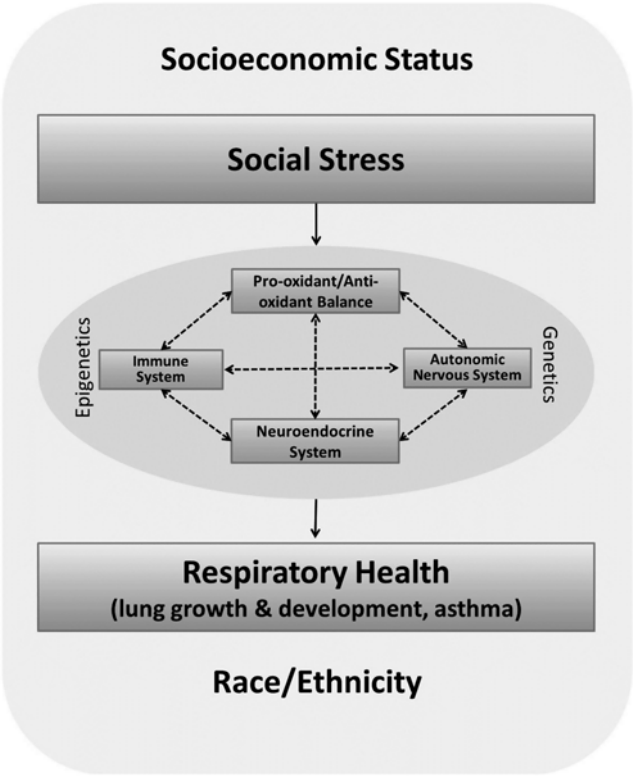

Fig. 8.1 Conceptual model linking social stress to lung growth/development and asthma

saccular units during the alveolar stage which starts late in pregnancy (beginning at ~34 to 36 weeks gestation) and continues postnatally over a period of several years. Over the first 2–3 years of life, the full complement of 23 airway generations and approximately 300 million alveoli are formed. Throughout early lung development, rapidly proliferating cells are most susceptible to the adverse effects of social and physical environmental factors that may impact many physiological systems underlying respiratory developmental processes [20]. Finally, there is a prolonged period of equilibrated lung growth that continues until body growth stops in late adolescence and early adulthood [21]. Gross changes in lung structure occur if development is disrupted during the embryonic phase which is characterized by a period of rapid cellular differentiation and morphogenesis. When late lung development is disrupted, lung architecture is malformed with consequent lung function changes. The underlying mechanisms leading to reduced lung function and exaggerated airway responsiveness involve chronic airway inflammation associated with a cycle of injury, repair, and remodeling [22, 23]. Furthermore, the fundamental cause of the airway inflammation is aberrant and/or excessive immune responses to various

social and physical environmental factors [22] and the most common cause of chronic airway inflammation in early childhood is arguably asthma. Notably, airway inflammation and remodeling begin and progress even in the presymptomatic state in early childhood [24, 25]. Given this and the fact that most of the extant research on social disparities in respiratory disease has centered on asthma [26–29], many of the principles presented herein will highlight asthma albeit they are more broadly applicable to other respiratory disorders.

Programming Stress Pathways Involved inRespiratory Disease

Critical Periods of Development and Perinatal Programming

It is essential to characterize mechanisms that lead to and maintain early predisposition if we want to identify individuals at risk for chronic respiratory disorders. Most respiratory conditions, including asthma and other chronic conditions, have their origin in early life. Immune and lung development occur largely in utero and during early childhood. Research continues to delineate early immunophenotypes and early airway response outcomes among children predisposed to asthma (atopic and nonatopic) and other chronic atopic disorders [30, 31]. Regulatory pathways that involve the collaboration of innate and adaptive immune responses are involved. Influences of factors outside the immune system, i.e., neurohormonal, autonomic nervous system (ANS), and mitochondrial function may also be involved. Plasticity is a consequence of environmental exposures (both social and physical) in critical periods affecting key physiological systems involved in developmental processes. Although both asthma and respiratory function are polygenic traits [32, 33], maternal factors in particular contribute to the intergenerational correlation [32, 34, 35]. That is, the risk of developing asthma is particularly increased if a positive parental history of atopy is present with effects being strongest for *maternal history* [34, 35]. Studies have also shown a greater correlation in forced expiratory volume in 1 s (FEV1) and other lung function parameters between mothers (compared with fathers) and offspring [32]. In addition to heritable traits, this may be due to perinatal programming—the influence of nongenetic or environmental factors in the perinatal period that organizes or imprints physiological systems. There is a growing list of environmental factors that may have programming effects including stress-induced changes in a number of molecular, cellular, and physiological states and their interrelating systems over development. As summarized below, in response to chronic stress, physiological systems may function at higher or lower levels than during typical homeostasis resulting in systems being permanently organized toward trajectories of poorer lung function and enhanced respiratory disease risk.

Immune System

Central to the pathophysiology of asthma phenotypes, as well as other respiratory diseases, are mechanisms of inflammation. These mechanisms overlap and may include immune-mediated inflammation associated with a Th2-biased response [36] and a tendency to produce immunoglobulin E (IgE) in response to environmental stimuli (e.g., allergens). The Th1–Th2 paradigm involves a complex interaction of T and B lymphocytes, resulting in the production of higher levels of particular cytokines, such as interleukin-4 (IL-4) or IL-13 and the more recently described IL-9, IL-25, and IL-31 as well as lower levels of interferon-γ (IFN-γ) [37]. Evidence suggests that those with early (i.e., starting in the first 2–3 years) sensitization to allergens are at greatest risk of developing chronic atopic disorders, airway inflammation, and obstruction [as reviewed in [38]]. While this paradigm has been useful in understanding the large fraction of subjects with allergic asthma, it is now recognized that the Th2-biased polarization of adaptive immunity is likely only one of numerous axes that give rise to heightened susceptibility to airway inflammation and altered reactivity [39]. Antigen-independent responses involving innate immune cells (e.g., bronchial epithelial cells, alveolar macrophages, and dendritic cells) may also be important [40, 41] and include novel cytokines (e.g., IL-17) [42]. Factors, including stress [41, 43], that disrupt maturation of local immune networks (e.g., dendritic cells [DCs], epithelial cells [ECs], regulatory T cells) may predispose to ongoing eosinophilic and neutrophilic inflammation.

These immune mechanisms have their roots in utero with an immunological bias toward a Th2 phenotype [44–50]. Immune programming can also be influenced by early postnatal environmental factors [51, 52]. Consequently, researchers have begun to examine in vitro responses of peripheral blood mononuclear cells (pBMCs) to allergens or mitogens to gain a better understanding of the immunodeviations that facilitate the manifestation of asthma and atopy in response to environmental factors [30]. The influence of stress on the timing and trajectory of these immunophenotypes and their relationship to the later development of clinical disorders, however, has only just begun to be studied. Prospective epidemiological studies have linked early life caregiver stress to dysregulation of immune function in a birth cohort predisposed to allergy, i.e., greater antigen-specific TNF-alpha production [53] and cord blood total IgE [54–56]. Interestingly, it has also been demonstrated that increased prenatal maternal stress is associated with increased IL-8 and TNF-α production following microbial stimulation suggesting that stress may operate through Toll-like receptor-dependent pathways [57]. Furthermore, low maternal childhood SES appears to be important for immune regulation and risk of adverse respiratory outcomes in children suggesting possible intergenerational effects [7].

Neuroendocrine and Autonomic Nervous Systems

Both glucocorticoid (GC) action and sympathovagal balance play a role in immunomodulation as well as fetal and postnatal lung development [38, 43, 58]. While research has made considerable strides toward the advancement of immune function assessment in the field of stress and respiratory diseases such as asthma [37, 53, 57, 59], studies assessing the hypothalamic–pituitary–adrenocortical (HPA) axis [60, 61] are infrequent and none consider the autonomic response in early development (i.e., pregnancy, early childhood). Increasingly, evidence suggests that autonomic imbalance or dysfunction, independent of neuroendocrine or hormonal abnormalities [62–64] may be an understudied factor in the expression of a number of respiratory disorders. Indeed, research implicating autonomic imbalance in the pathogenesis of inflammatory and hypersensitivity reactions in the nose, skin, and the lung spans more than four decades [65–67]. This is because the ANS is integrally involved in regulation of airway function [68] and has important ties to immunoregulation. Notably, the HPA axis and ANS seem particularly susceptible to stress-induced programming.

Animal and human studies support the connection between an adverse intrauterine environment as well as experiences in early postnatal life and alterations of ANS functioning (e.g., sympathovagal balance) [69–72]. Animal research suggests that neural control of airway smooth muscle and irritant receptor systems is sensitive to environmental programming [69]. Respiratory and vagal systems undergo postnatal maturation to form an integration of respiratory and cardiovascular function [73, 74]. While our knowledge about the vulnerability of these systems to perinatal environmental influences and early programming is scarce [75], prenatal stress can increase allergen-induced airway inflammation [76, 77] and airway hyperresponsiveness (AHR) in prenatally stressed mice [78]. Others show exacerbations in airway inflammation in OVA-sensitized rats following repeated psychosocial challenge [79–83].

In humans, autonomic responses show developmental changes with relative stability between 6 and 12 months of age [84]. It seems reasonable that disruption of neuroendocrine and vagal anti-inflammatory pathways may predispose some individuals to immunodeviations and consequent disproportionate inflammatory responses resulting in altered respiratory responses. Balancing functional parasympathetic and sympathetic activity, in relation to emotional stimuli and immune function, may be central to understanding how psychological stressors influence airway inflammation and enhanced airway reactivity. Unfortunately, this has not been examined in human research. Nonetheless, reversible airway obstruction has been demonstrated during psychological challenge; cholinergic blockade supports a vagal origin [85, 86]. Negative affect in particular increases airway resistance [87] and it is suggested this occurs through vagal excitation to the airways [88]. Airway responses to induction of depressed mood are correlated with increased respiratory sinus arrhythmia (RSA) in asthmatics [89, 90]. Individuals with a propensity toward a greater vagal system response to distress may be prone to exaggerated airway

narrowing. Interestingly, in an urban pregnancy cohort designed to study the effects of prenatal maternal and early life stress on urban childhood asthma risk, differential stress reactivity as indexed by prenatal HPA axis disruption [91] and cardiorespiratory parameters in infancy [92] has been observed.

Growing evidence also implicates a number of neurotrophins (NTs) as mediators or moderators of allergic disorders [93, 94] and shows that NT expression and signaling may be influenced by stress [95, 96]. One study in subjects with allergic asthma demonstrated that increased psychological stress was correlated with increased levels of brain-derived neurotrophic factor (BDNF) which, in turn, was negatively correlated with percent predicted forced expiratory volume in 1 s (FEV_1) [97]. Notably, stress perception was also positively correlated with the percentage of TNF-alpha-producing T cells in these subjects. The authors suggest that this may indicate a neuroimmunological interaction given the ubiquitous secretion of BDNF in human peripheral blood monocytes which was enhanced when stimulated with TNF-alpha [98]. This group has also demonstrated stress-induced increase in tachykinin-like substance P associated with allergic airway inflammation in a mouse model [99].

Glucocorticoid resistance is an alternative hypothesis linking stress, neuroendocrine disruption (i.e., HPA axis), and immune function [100, 101]. Insight into the cellular and molecular mechanisms fundamental to stress-induced steroid resistance is provided in several studies. Oxidative stress pathways are likely involved in pathways linking psychosocial stress and respiratory diseases such as asthma [102] as well as steroid resistant asthma [103, 104]. This may be particularly applicable to airway inflammation where neutrophilic rather than eosinophilic inflammation predominates [105, 106]. Indeed, oxidative stress has been shown to contribute to steroid resistance in the context of neutrophilic inflammation in a mouse model of acute asthma exacerbations [107] supporting this hypothesis. While human data in the context of lung disease are sparse in this regard, one recent cross-sectional analysis in adolescents demonstrated that pBMCs harvested from asthmatics who perceived low parental support (i.e., greater stress) were more resistant to hydrocortisone's effects on cytokine expression (IL-5, IFN-γ) and activation of eosinophils relative to asthmatics reporting higher parental support [108]. Further, glucocorticoid resistance disproportionately affects minority and low-income pregnant women [109] resulting in a limited ability to regulate inflammation. Examination of mechanisms contributing to steroid resistance in relation to increased environmental stressors may provide insight into the relationship between social stress, respiratory disease, and AHR across populations.

Oxidative Stress

While the mechanisms underlying environmental toxicities contributing to altered lung growth starting in utero are not fully elucidated, many lines of research point to a central role of oxidative stress and redox imbalance. Because reactive oxygen species (ROS) are thought to play a role in the etiology of disrupted lung growth and

a number of respiratory disorders, in utero and early life exposures that promote (or diminish) the antioxidant defense system of the offspring may have lasting impacts. For example, studies show that factors that enhance antioxidant defense during pregnancy may have a persistent effect on antioxidant capacity that may mitigate oxidative stress-induced DNA damage later in life in tissues including the lung [110]. Social stress, like tobacco smoke exposure, is a pro-oxidant and may thus operate through these same pathways [102]. Parallel to research on intrauterine tobacco smoke exposure, epidemiological studies link increased prenatal stress with poor somatic growth [111–113]. This in turn is associated with smaller lungs and hence smaller airways, which also increase the risk of respiratory viral infections, altered lung function, wheeze, and other respiratory disorders [114, 115].

Emerging biomarkers of systemic oxidative stress include mitochondrial changes [116]. Mitochondria are major intracellular sources and primary targets of ROS, making them particularly susceptible to even small increases in systemic ROS [117]. Mitochondrial function can be altered by oxidative stress and inflammation [118]. In turn, dysfunctional mitochondria produce additional oxidation that may sustain systemic oxidative stress [118]. Alterations in mitochondrial function in the airway epithelium may intensify oxidative stress effects [119] suggesting mitochondrial-dependent pathways are important for airway remodeling and ultimately respiratory disease development [120]. Given that social stress has been shown to induce oxidative stress and damage [121], mitochondriomic changes may serve not only as a mechanistic function in the pathway from exposure to disease, but also as a "biomarker of stress." Recent studies have implicated mitochondrial dysfunction in the etiology and symptomatology of many respiratory diseases [122–125]. Elevated serum lactate, an indicator of mitochondrial dysfunction [126], has been linked to both stable and acute severe asthmatic phenotypes [123, 124]. Variations in mitochondrial DNA have also been associated with elevated total serum IgE levels and augmenting Th2-type responses suggesting a role in the development of adaptive immunity [122, 127]. Mitochondrial changes have also been linked to the development and modulation of COPD, cystic fibrosis, and cancer [125]. Further, early life stress has been shown to induce mitochondrial changes via adenosine triphosphate (ATP) release and mitochondrial oxygen consumption [128, 129] suggesting alterations in these specific subcellular components likely play a role in stress-induced effects on the developing respiratory system and disease expression.

In addition to disparities in glucocorticoid resistance, high levels of oxidative stress, as measured by gamma-glutamyltransferase, a correlate of biologic exposure to pro-oxidant producing toxins [130], also disproportionately affect individuals of lower SES (education, occupational class, income). Similarly, increasing evidence suggests that minorities may be more likely to experience enhanced oxidative stress, oxidative DNA damage, and inflammation in response to environmental stimuli [131, 132]. These data suggest that the racial disparities and increasing prevalence of asthma, and other respiratory conditions, with decreasing SES may result from higher levels of oxidative stress among persons of lower relative to higher status and minorities.

Genetics and Epigenetics

Genetic factors of potential importance include those that influence immune development and airway inflammation in early life, corticosteroid regulatory genes, adrenergic system regulatory genes, biotransformation genes, and cytokine pathway genes. Variants of the glucocorticoid receptor gene have been shown to contribute to interindividual variability in HPA axis activity and glucocorticoid sensitivity in response to stress [133, 134]. Studies related to factors regulating the feedback mechanisms involved in the glucocorticoid response to stress are also of interest [135]. A recent study examined polymorphisms of the TNF-alpha promoter region (TNF-308G/A) and linked specific variants to increased C-reactive protein (CRP), a proinflammatory marker [136]. These are potentially interesting candidate genes to include in future studies of risk for atopic disease. Such studies that consider gene x environment interactions (i.e., stress by pathway genes) may inform specific mechanisms related to stress and atopy.

Programming effects of stress on respiratory outcomes may operate at a more fundamental molecular level, i.e., through epigenetic programming. Epigenetics may be at the roots of developmental plasticity imprinting environmental experiences on the fixed genome [137] albeit data are scare for respiratory health and allergic disorders [138, 139]. The epigenetic landscape has multiple layers, comprising of histone modifications, ncRNA, nucleosome positioning, and DNA methylation (the most studied epigenetic mechanism). In particular, DNA methylation is an adaptable epigenetic mechanism that modifies genome function through the addition of methyl groups to cytosine to form 5-methyl-cytosine (5mC). DNA methylation marks are largely established early in life [140] and may ensure stable regulation that mediates persistent changes in biological and behavioral phenotypes over the lifespan. Determining the range of environmental exposures that impact the epigenome during development was a research priority identified at the recent NHLBI *Pediatric Pulmonary Disease Strategic Planning Workshop* [141]. DNA methylation of many genes changes with disease status and in response to environmental signals including chemical exposures such as diet, drugs, and toxins. Recent findings also implicate psychological stress given behavioral studies demonstrating epigenetic changes during fear conditioning [142, 143] and evidence for epigenetic programming related to maternal care [144, 145].

The epigenome may be particularly sensitive to dysregulation in early development when DNA synthesis rates are highest. Genes involved in hypothalamic–pituitary–adrenal (HPA) axis functioning seem particularly susceptible to stress-related programming [146]. These include glucocorticoid receptor expression, the activation of which alters HPA activity through negative feedback inhibition. The human glucocorticoid receptor (GR) promoter region is extensively methylated with diverse methylation profiles demonstrated in normal donors [147]. The intracellular access of glucocorticoids to their receptors is also modulated by the 11 beta-hydroxysteroid dehydrogenase (11βHSD) enzymes, which interconvert biologically active 11 β-hydroxyglucocorticoids and inactive 11-ketosteroids [148]. While compromised

11βHSD2 activity can be caused by loss-of-function mutations of the gene encoding 11βHSD2, the frequency of such mutations is extremely low. Thus, other mechanisms accounting for the interindividual variability in 11βHSD2 enzyme activity should be considered. The 11βHSD2 promoter comprises a highly G+C-rich (or GC-rich) core, contains more than 80 % GC, lacks a TATA-like element, and has two typical CpG islands raising the possibility that methylation may play a role in the epigenetically determined interindividual variable expression of 11βHSD2.

Another candidate pathway implicated in both airway inflammation [149] and autonomic response [150] is the nitric oxide (NO) signaling pathways. Alterations of NO expression occur in the context of psychological stress and stress-related behaviors [151]. The inducible nitric oxide synthase (NOS) genes are also susceptible to epigenetic programming [152].

The notion that variability in methylation between subjects may reflect an important epigenetic mechanism is suggested by recent studies in both animals and humans. Epigenetic modulation of the 11βHSD2 gene has been recently demonstrated in a rodent model and cultured cell lines [153], albeit epigenetic regulation of this gene is not well characterized in humans. Weaver and colleagues have demonstrated differential methylation patterns of the NGFI-A-binding site in GR promoter 1_7 in the rat brain in offspring that had received poor maternal care versus those that had received better maternal care [154]. When pups were cross-fostered between dams providing good or poor postnatal care, the pups developed the epigenome of the foster mother. This same group reported increased methylation in a neuron-specific GC receptor (NR3C1) promoter as well as decreased levels of GC receptor mRNA from hippocampus tissue obtained from suicide victims with a history of childhood abuse [155]. Similar postnatal care has been linked to several hypermethylated regions upstream and downstream of the proximal GR promoter [156]. Recent human data demonstrates that methylation of exon 1 F in fetal cord blood was sensitive to maternal mood in the perinatal period and the infants HPA stress reactivity [157].

As highlighted earlier, the expression of neurotrophins, specifically BDNF, contributes to normal airway structure and function, and to airway hyperreactivity and remodeling in respiratory diseases. As reviewed by Prakash and Martin [158], sustained stress has been linked to hypermethylation of the *BDNF* gene, an effect which has been shown to begin in infancy and persist into adulthood, and consistently reduce BDNF mRNA and protein levels. Although early life adversity appears to influence the epigenetic markings of the *BDNF* gene, the underlying mechanisms are not completely clear.

In summary, genetic and epigenetic studies tell us that exposure to altered glucocorticoid receptor response through early development, even beginning in utero, programs major changes in the endogenous neuroendocrine and immune mechanisms that may, in turn, lead to increased vulnerability to respiratory disease. Whether alterations in DNA methylation underlie stress-induced phenotypic plasticity related to lung structure and function or disease risk remains largely unexplored in ethnically diverse populations. It will be important to begin to understand factors related to developmental programming of glucocorticoid sensitivity during critical periods of development which may play a role in disease etiology as well as subsequent morbidity.

Role of Stress in Respiratory Disease Morbidity: Asthma as an Evidence-Based Example

While asthma affects people of all ages, races, and ethnic groups, in the United States (U.S.), morbidity disproportionately burdens poor, ethnic minorities in both urban and nonurban environments [28, 29, 159]. Low SES has been consistently associated with greater asthma impairment, including more frequent emergency department visits [26] and greater symptoms/morbidity [27]. Similarly, racial/ethnic differences in asthma prevalence, asthma attacks, and increased emergency room visits for asthma exist among children and adults [160].

Asthma exacerbations are influenced by numerous factors including psychosocial influences [161, 162]. Trueba and Ritz [163] published an extensive review concluding individuals with existing asthma experiencing stress express a stronger bias toward Th2 activation. This is in line with the theory that stress effects Th cell functioning negatively increasing the risk of asthma exacerbations. The basic premise is that psychological stress can heighten airway inflammation in response to environmental triggers, and consequently increase the frequency, duration, and severity of an individual's symptoms [164].

Low SES is consistently associated with greater asthma impairment, including more frequent emergency department visits, hospitalizations, greater symptoms, and more severe asthma [8, 165, 166], findings which are consistent regardless of the SES measure being explored. Ungar and colleagues [166] report that children with high income adequacy experience up to 28 % fewer exacerbations than children with low income adequacy and that every percentage increase in the proportion of income spent out of pocket on asthma medications was associated with a 14 % increase in exacerbations.

How does social stress help explain this observation? Poorer asthma morbidity may be greater among individuals of lower SES because they bear a disproportionate burden of exposure to suboptimal, unhealthy socially toxic environments. For example, in a study examining stressors immediately before or during pregnancy among a sample of 143,452 women [167], stress exposure increased as income decreased, with 57 % of low-income women experiencing at least one chronic stressor [e.g., economic hardship (37 %), job loss (19 %), separation or divorce (15 %), incarceration of partner (8 %), and domestic violence (5 %)]; 29 % experienced multiple stressors concurrently. In 2014, a study was published which explored the role of financial and social hardships in asthma racial disparities [28]. Compared to whites, African American caregivers experienced more social hardships including lower income and education attainment, difficulty finding work, having no one to borrow money from, not owning a car, and being single/never married. They reported that the SES and hardships explained 49 % of the observed racial disparity in asthma morbidity defined as hospital readmission. Effects of these stress exposures may be compounded among minorities by racism-related stressors.

Traumatic stressors may warrant particular consideration for many reasons [146]. Trauma, like other stress, occurs at increased rates among low-income, minority populations [168, 169]. Holman and colleagues [169] examined the rates of trauma in an ethnically diverse, community-based sample ($N = 1456$). Nearly 10 % experienced a trauma in the past year; 57 % reported at least one lifetime event including interpersonal violence occurring outside the family (21 %), acute losses or accidents (17 %), witnessing death or violence (13 %), and domestic violence (12 %). Hien and Bukszpan [170] examined lifetime interpersonal violence among a "control" group of urban, low-income women, predominantly Latina or blacks, who had been screened for the absence of psychopathology. Almost 28 % of these urban women reported a history of childhood abuse, compared to general population estimates of 10 %. Urban minority women also experience heightened levels of community violence [171, 172]. Other studies have documented increased rates of PTSD and depression in urban samples [146]. The perinatal period is a vulnerable time to experience more intense psychological symptoms, particularly for low-income women. Compared to other forms of stress, trauma is more likely to result in psychological morbidity [e.g., posttraumatic stress disorder (PTSD), depression] and persistent psychophysiological changes (HPA axis, sympathetic-adrenal-medullary [SAM] system). One study in urban children found a relationship between exposure to chronic stress (violence) in early childhood and reduced lung function at age 6 years [173] suggesting these effects persist years after exposure, particularly when the exposure occurs during a critical developmental window (e.g., when stress regulatory systems are developing).

Need for a Multilevel Framework

The etiology of respiratory health problems is increasingly recognized as a result of the complex interplay of influences operating at several levels, including the individual, the family, and the community (Fig. 8.2). Ecological views on health recognize that individual-level health risks and behaviors have multilevel determinants, in part influenced by the social context within which subjects live [174]. That is, chronic stress experiences are significantly influenced by the characteristics of the families, homes, and communities in which we live [175, 176]. Both physical and social factors can be a source of environmental demands that contribute to stress experienced by populations living in a particular area [177].

Taking a multilevel approach to examining stress effects on respiratory disease development, including asthma, may be particularly relevant to the understanding of disparities based on race/ethnicity and SES [176]. This includes an environmental justice perspective underscoring the role of structural and macrosocial forces that shape exposure and vulnerability to diseases may better inform the complex social patterning of asthma [176]. According to this framework, asthma rates are higher and the associated morbidity is greater among the poor because they bear a disproportionate burden of exposure to suboptimal, unhealthy environmental conditions. Upstream social and economic factors determine differential exposures to relevant

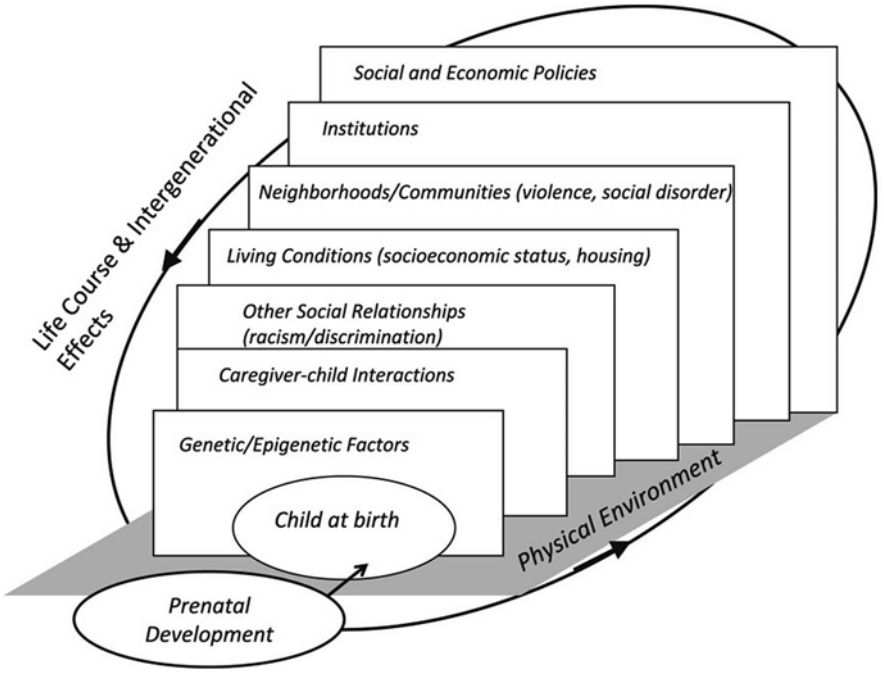

Fig. 8.2 Characterizing stress across the life course: an ecological approach

asthma pathogens and toxicants [16]. Also, understanding the upstream factors (e.g., social and economic policies) that contribute to the varying social conditions for populations and individuals being studied will better inform needed interventions.

Life Course Perspective and Intergenerational Effects

Other studies provide evidence supporting the intergenerational transmission of psychophysiological vulnerability in traumatized populations. While studies of maternal stress and infant outcomes typically examine events occurring during pregnancy, we recently considered stress (interpersonal trauma, IPT) across the mother's life course in relation to early immune markers in their children [178]. The life course perspective posits that some stressors may influence health through two mechanisms, early programming and cumulative pathways, in addition to more immediate effects. Early programming may occur if exposures during sensitive developmental periods in the mother have lasting psychobiologic sequelae. Exposure to IPT in earlier life can generate disrupted physiological stress responses even several years following the trauma. Thus, maternal IPT may be linked to infant health through more latent effects (i.e., lasting effects from abuse in childhood/

adolescence), proximate effects (i.e., trauma experienced in or around the pregnancy), and cumulative life course effects (i.e., allostatic load of accumulated traumas over the mother's life). It has been demonstrated that infants born to mothers with chronic trauma exposure—that is, both early in life and more proximate to the pregnancy—would be at greatest risk of expressing elevated IgE [178].

Constricting Communities

Indicators of neighborhood disadvantage, characterized by the presence of a number of area-level stressors including poverty, unemployment/underemployment, percentage of unskilled laborers, limited social capital or social cohesion, substandard housing, and high crime/violence exposure rates, have been investigated in relation to urban children's development [176]. Such stress is chronic and can affect all subjects in a given environment regardless of their individual-level risks.

Growing evidence suggests that community violence, a risk factor experienced disproportionately by lower SES individuals, may contribute to the burden of asthma in urban populations. This notion is supported by three longitudinal studies. Sternthal et al. [179] analyzed over 2000 urban children in Chicago between the ages of 0 and 9 and reported a significant association between higher community violence exposure and increased risk for asthma development in urban children. This association was robust after controlling for important individual-level factors (race/ethnicity, SES, maternal health behaviors, family violence) and neighborhood-level confounders (concentrated disadvantage, social disorder, and collective efficacy). In an ethnic minority population made up of mainly low SES participants, Chiu and colleagues [180] observed independent effects of prenatal community violence exposure and physical toxins at the neighborhood level (e.g., air pollution) on repeated wheeze. Similarly, lifetime community violence exposure among ethnically diverse 6- to 7-year-olds has been linked to poorer lung function (e.g., lower FEV_1) [173]. In addition to asthma development and lung function detriments, increased exposure is also associated with higher hospitalization rates and emergency department visits [181].

Housing Stressors

A number of subjective housing characteristics have been linked to adverse psychological outcomes. This subjective emotional dimension of housing may influence asthma outcomes [8, 182] although this is only starting to be empirically explored. Specifically, housing stress related to lack of utilities, furniture, appliances, and relationships with neighbors/landlords has been linked to poor asthma control, school absences, unplanned visits to the emergency department, and exercise intolerance [183]. Further, housing disarray, characterized by a dark, cluttered, crowded,

or noisy house, has been associated with increased asthma prevalence among children [184]. Studies have shown that improved housing can have a positive impact on asthma severity including decreases in lost school/work days, disturbed sleep, and asthma symptoms [185]. Improving housing should be a focus for any intervention efforts.

Family Factors

There have been a number of examples from the asthma epidemiology literature showing associations between early caregiver stress and the development of asthmatic phenotypes in early childhood [186, 187]. Suglia and colleagues [188] recently demonstrated that maternal ability to maintain positive caregiving processes in the context of even more extreme stress may buffer the effects on child asthma risk. They examined the prospective relationship between maternal intimate partner violence (IPV) and asthma onset in children in the Fragile Families and Child Wellbeing Study ($N=3117$), a birth cohort. Maternal report of IPV was assessed after the child's birth and at 12 and 36 months. Mothers also indicated how many days a week they participated in activities with the child and the amount and type of educational/recreational toys available for the child. Maternal report of physician-diagnosed asthma by age 36 months was the outcome. In adjusted analysis, children of mothers experiencing IPV chronically (at all time periods), compared to those not exposed, had a twofold increased risk of developing asthma. In stratified analysis, children of mothers experiencing IPV and low levels of mother–child activities (RR 2.7, 95 % CI 1.6, 4.7) had a significant increased risk for asthma. Those exposed to IPV and high levels of mother–child activities had a lower risk for asthma (RR 1.6, 95 % CI 0.9, 3.2). One should also consider the developmental timing of exposures over the life course relative to specific asthma outcomes whether individual or contextual factors are being considered. Factors leading to the onset, remission, or persistence of asthma across the life course may be influenced by social experiences and physical exposures beginning in utero, a series of social and biologic experiences initiated by early childhood exposure or cumulative exposure to toxic biologic or social factors over critical periods of development. It is important to consider stress at these multiple levels given that they are interrelated throughout the life course. If we can understand at what level stress is occurring and perhaps has the greatest impact on asthma expression, this may inform the most effective interventions.

Stress-Enhancing Effects on Physical Environmental Exposures

Because of the covariance across exposures and evidence that social stress and other environmental toxins (e.g., pollutants, tobacco smoke) may influence common physiological pathways (e.g., oxidative stress, pro-inflammatory immune pathways,

autonomic disruption), understanding the potential synergistic effects promises to more completely inform children's asthma risk [15]. Epidemiological studies have demonstrated synergistic effects of stress and air pollution on asthma expression among children and adolescents [180, 189–191]. We need to better understand how the physical and psychological demands of living in a relatively deprived environment may potentiate an individual's susceptibility to cumulative exposures across these domains.

Summary

Social toxicity experienced as increased psychological stress is likely a major driver of observed disparities in lung growth and development and asthma, as well as a range of other respiratory conditions. Most respiratory conditions likely share overlapping etiology; therefore, multiple mechanistic pathways with complex interdependencies must be considered when examining the integrative influence of stress independently as well as the interaction of social and physical environmental toxins in explaining the social patterning of respiratory diseases. Because these factors tend to cluster in the most socially disadvantaged, this line of research may better inform the etiology of growing health disparities increasingly documented for respiratory disorders. Future epidemiologic studies which concomitantly consider social stress as well as physical environmental toxins will likely more fully explain the etiology of respiratory disease disparities as well as inform more effective prevention and intervention strategies that enhance lung growth and reduce respiratory disease morbidity.

Acknowledgements During preparation of this chapter KJ Brunst was supported by the National Institutes of Health, K99ES024116.

References

1. Castro-Diehl C, Diez Roux AV, Seeman T, Shea S, Shrager S, Tadros S. Associations of socioeconomic and psychosocial factors with urinary measures of cortisol and catecholamines in the Multi-Ethnic Study of Atherosclerosis (MESA). Psychoneuroendocrinology. 2014;41:132–41.
2. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. Int J Epidemiol. 2011;40(3):804–18.
3. Lorant V, Deliege D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. Am J Epidemiol. 2003;157(2):98–112.
4. Schraufnagel DE, Blasi F, Kraft M, Gaga M, Finn PW, Rabe KF, et al. An official American Thoracic Society/European Respiratory Society policy statement: disparities in respiratory health. Am J Respir Crit Care Med. 2013;188(7):865–71.

5. Harik-Khan RI, Muller DC, Wise RA. Racial difference in lung function in African-American and White children: effect of anthropometric, socioeconomic, nutritional, and environmental factors. Am J Epidemiol. 2004;160(9):893–900.
6. Van Sickle D, Magzamen S, Mullahy J. Understanding socioeconomic and racial differences in adult lung function. Am J Respir Crit Care Med. 2011;184(5):521–7.
7. Sternthal MJ, Coull BA, Chiu YH, Cohen S, Wright RJ. Associations among maternal childhood socioeconomic status, cord blood IgE levels, and repeated wheeze in urban children. J Allergy Clin Immunol. 2011;128(2):337–45.e1.
8. Schreier HM, Chen E. Socioeconomic status and the health of youth: a multilevel, multidomain approach to conceptualizing pathways. Psychol Bull. 2013;139(3):606–54.
9. McLaughlin KA, Costello EJ, Leblanc W, Sampson NA, Kessler RC. Socioeconomic status and adolescent mental disorders. Am J Public Health. 2012;102(9):1742–50.
10. Rudd RE, Zobel EK, Fanta CH, Surkan P, Rodriguez-Louis J, Valderrama Y, et al. Asthma: in plain language. Health Promot Pract. 2004;5(3):334–40.
11. Eisner MD, Katz PP, Yelin EH, Shiboski SC, Blanc PD. Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. Respir Res. 2001;2(1):53–60.
12. Kanervisto M, Vasankari T, Laitinen T, Heliovaara M, Jousilahti P, Saarelainen S. Low socioeconomic status is associated with chronic obstructive airway diseases. Respir Med. 2011;105(8):1140–6.
13. Eisner MD, Blanc PD, Omachi TA, Yelin EH, Sidney S, Katz PP, et al. Socioeconomic status, race and COPD health outcomes. J Epidemiol Community Health. 2011;65(1):26–34.
14. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007;298(14):1685–7.
15. Wright RJ. Moving towards making social toxins mainstream in children's environmental health. Curr Opin Pediatr. 2009;21(2):222–9.
16. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. Pediatrics. 2009;123 Suppl 3:S174–84.
17. Pinkerton KE, Joad JP. Influence of air pollution on respiratory health during perinatal development. Clin Exp Pharmacol Physiol. 2006;33:269–72.
18. Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, et al. Developmental plasticity and human health. Nature. 2004;430:419–21.
19. Kajekar R. Environmental factors and developmental outcomes in the lung. Pharmacol Ther. 2007;114(2):129–45.
20. Bateson TF, Schwartz J. Children's response to air pollutants. J Toxicol Environ Health Part A. 2008;71(3):238–43.
21. Warburton D, El Hashash A, Carraro G, Tiozzo C, Sala F, Rogers O, et al. Lung organogensis. Curr Top Dev Biol. 2010;90:73–158.
22. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. J Allergy Clin Immunol. 2005;116(1):16–24.
23. Holgate ST. Asthma: a dynamic disease of inflammation and repair. In: Chadwick DJ, Cardew G, editors. The rising trends in asthma. Ciba Foundation symposium 206. West Sussex: Wiley; 1997. p. 5–34.
24. Pohunek P, Warner JO, Turzikova J, Kudrmann J, Roche WR. Markers of eosinophilic inflammation and tissue re-modelling in children before clinically diagnosed bronchial asthma. Pediatr Allergy Immunol. 2005;16(1):43–51.
25. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172(10):1253–8.
26. Law HZ, Oraka E, Mannino DM. The role of income in reducing racial and ethnic disparities in emergency room and urgent care center visits for asthma-United States, 2001-2009. J Asthma. 2011;48(4):405–13.

27. Thakur N, Martin M, Castellanos E, Oh SS, Roth LA, Eng C, et al. Socioeconomic status and asthma control in African American Youth in SAGE II. J Asthma. 2014;51:720–8.
28. Beck AF, Huang B, Simmons JM, Moncrief T, Sauers HS, Chen C, et al. Role of financial and social hardships in asthma racial disparities. Pediatrics. 2014;133(3):431–9.
29. Hill TD, Graham LM, Divgi V. Racial disparities in pediatric asthma: a review of the literature. Curr Allergy Asthma Rep. 2011;11(1):85–90.
30. Heaton T, Rowe J, Turner S, Salberse RC, de Klerk N, Suriyaarahchi D, et al. An immunoepidemiological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children. Lancet. 2005;365:142–9.
31. Saglani S, Bush A. The early-life origins of asthma. Curr Opin Allergy Clin Immunol. 2007;7(1):83–90.
32. Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Differences in familial segregation of FEV1 between asthmatic and nonasthmatic families: role of maternal component. Am J Respir Crit Care Med. 1998;158:162–9.
33. Kumar A, Ghosh B. Genetics of asthma: a molecular biologist perspective. Clin Mol Allergy. 2009;7:7.
34. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? Am J Respir Crit Care Med. 1998;158(1):176–81.
35. Bjerg A, Hedman L, Perzanowski MS, Platts-Mills T, Lundback B, Ronmark E. Family history of asthma and atopy: in-depth analyses of the impact on asthma and wheeze in 7- to 8-year-old children. Pediatrics. 2007;120(4):741–8.
36. Mossman TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today. 1996;17:138–46.
37. Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. J Allergy Clin Immunol. 2010;125:S53–72.
38. Wright RJ. Perinatal stress and early life programming of lung structure and function. Biol Psychol. 2010;84:46–56.
39. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. Th2-driven inflammation defines major sub-phenotypes of asthma. Am J Respir Crit Care Med. 2009;180:388–95 [Epub ahead of print].
40. Suarez CJ, Parker NJ, Finn PW. Innate immune mechanism in allergic asthma. Curr Allergy Asthma Rep. 2008;8(5):451–9.
41. Joachim RA, Handjiski B, Blois SM, Hagen E, Paus R, Arck PC. Stress-induced neurogenic inflammation in murine skin skews dendritic cells towards maturation and migration. Key role of intercellular adhesion molecule-1/leukocyte function-associated antigen interactions. Am J Pathol. 2008;173:1379–88.
42. Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol. 2010;10:479–89 [Epub ahead of print].
43. Wright RJ. Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk. Pediatr Perinat Epidemiol. 2007;21:8–14.
44. Peden DB. Development of atopy and asthma: candidate environmental influences and important periods of exposure. Environ Health Perspect. 2000;108 Suppl 3:475–82.
45. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. Clin Exp Allergy. 2002;32(1):43–50.
46. Devereux G, Seaton A, Barker RN. In utero priming of allergen-specific helper T cells. Clin Exp Allergy. 2001;11:1686–95.
47. Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. J Immunol. 1998;160:4730–7.
48. Miles EA, Warner JA, Jones AC, Colwell BM, Bryant TN, Warner JO. Peripheral blood mononuclear cell proliferative responses in the first year of life in babies born to allergic parents. Clin Exp Allergy. 1996;26:780–8.

49. Liao SY, Liao TN, Chiang BL, Huang MS, Chen CC, Chou CC, et al. Decreased production of IFN gamma and increased production of IL-6 by cord blood mononuclear cells of newborns with a high risk of allergy. Clin Exp Allergy. 1996;26:397–405.
50. Tang MLK, Kemp AS, Thorburn J, Hill DJ. Reduced interferon-gamma secretion in neonates and subsequent atopy. Lancet. 1994;344:983–5.
51. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. J Allergy Clin Immunol. 2003;111:661–75.
52. Willwerth BM, Schaub B, Tantisira KG, Gold DR, Palmer LJ, Litonjua AA, et al. Prenatal, perinatal, and heritable influences on cord blood immune responses. Ann Allergy Asthma Immunol. 2006;96:445–53.
53. Wright RJ, Finn PW, Contreras JP, Cohen S, Wright RO, Staudenmayer J, et al. Chronic caregiver stress and IgE expression, allergen-induced proliferation and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol. 2004;113:1051–7.
54. Peters JL, Cohen S, Staudenmayer J, Hosen J, Platts-Mills TA, Wright RJ. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. Allergy. 2012;67(4):545–51.
55. Lin YC, Wen HJ, Lee YL, Guo YL. Are maternal psychosocial factors associated with cord immunoglobulin E in addition to family atopic history and mother immunoglobulin E? Clin Exp Allergy. 2004;34(4):548–54.
56. Reyes M, Perzanowski MS, Whyatt RM, Kelvin EA, Rundle AG, Diaz DM, et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. Ann Allergy Asthma Immunol. 2011;107(1):42–9.e1.
57. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. Am J Respir Crit Care Med. 2010;182(1):25–33.
58. Bolt RJ, van Weissenbruch MM, Lafever HN, Delemarre-van de Waal HA. Glucocorticoids and lung development in the fetus and preterm infant. Pediatr Pulmonol. 2001;32:76–91.
59. Chen E, Fisher EB, Bacharier LB, Strunk RC. Socioeconomic status, stress, and immune markers in adolescents with asthma. Psychosom Med. 2003;65(6):984–92.
60. Buske-Kirschbaum A. Cortisol responses to stress in allergic children: interaction with the immune response. Neuroimmunomodulation. 2009;16:325–32.
61. Wright RJ, Schreier HM. Seeking an integrated approach to assessing stress mechanisms related to asthma: is the allostatic load framework useful? Am J Respir Crit Care Med. 2013;187(2):115–6.
62. Licht CMM, Breeburg SA, van Reedt Dortland AKB, Giltay EJ, Hoogendjik WJG, DeRijk RH, et al. Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities. Endocr Res. 2010;95:2458–66.
63. Yun AJ, Bazar KA, Lee PY. Autonomic dysfunction may be an under-recognized cause of female fertility disorders. Med Hypotheses. 2004;63:172–7.
64. Jankowska EA, Ponikowski P, Piepoli MF, Banasiak W, Anker SD, Poole-Wilson PA. Autonomic imbalance and immune activation in chronic heart failure—pathophysiological links. Cardiovasc Res. 2006;70:434–5.
65. Milles JE, Widdicombe JG. Role of the vagus nerves in anaphylaxis and histamine-induced bronchoconstrictions in guinea-pigs. Br J Pharmacol. 1970;39:724–31.
66. Baraniuk JN, Silver PB, Kaliner MA, Barnes PJ. Perennial rhinitis subjects have altered vascular, glandular, and neural responses to bradykinin nasal provocation. Int Arch Allergy Immunol. 1994;103:202–8.
67. Ko JH, Kuo TB, Lee GS. Effect of postural change on nasal airway and autonomic nervous system established by rhinomanometry and heart rate variability analysis. Am J Rhinol Allergy. 2008;22:159–65.
68. Wright RJ. Stress-related programming of autonomic imbalance: role in allergy and asthma. Chem Immunol Allergy. 2012;98:32–47.

69. Card JP, Levitt P, Gluhovsky M, Rinaman L. Early experience modifies the postnatal assembly of autonomic emotional motor circuits in rats. J Neurosci. 2005;25(40):9102–11.
70. Jansson T, Lambert GW. Effect of intrauterine growth restriction on blood pressure, glucose tolerance and sympathetic nervous system activity in the rat at 3-4 months of age. J Hypertens. 1999;17(9):1239–48.
71. Pryce CR, Ruedi-Bettschen D, Dettling AC, Feldon J. Early life stress: long-term physiological impact in rodents and primates. News Physiol Sci. 2002;17:150–5.
72. Herlenius E, Lagercrantz H. Development of neurotransmitter systems during critical periods. Exp Neurol. 2004;190 Suppl 1:S8–21.
73. Carroll JL. Developmental plasticity in respiratory control. J Appl Physiol. 2003;94:375–89.
74. Eckberg DL. The human respiratory gate. J Physiol. 2003;548:339–52.
75. Bavis RW, Mitchell GS. Long-term effects of the perinatal environment on respiratory control. J Appl Physiol. 2008;104(4):1220–9.
76. Nogueira PJ, Ferreira HHA, Antunes E, Teixeira NA. Chronic mild prenatal stress exacerbates the allergen-induced airway inflammation in rats. Mediat Inflamm. 1999;8:119–22.
77. Quarcoo D, Pavlovic S, Joachim RA. Stress and airway reactivity in a murine model of allergic airway inflammation. Neuroimmunomodulation. 2009;16:318–24.
78. Pincus-Knackstedt MK, Joachim RA, Blois SM, Douglas AJ, Orsal AS, Klapp BF, et al. Prenatal stress enhances susceptibility of murine adult offspring toward airway inflammation. J Immunol. 2006;177(12):8484–92.
79. Datti F, Datti M, Antunes E, Teixeira NA. Influence of chronic unpredictable stress on the allergic responses in rats. Physiol Behav. 2002;77(1):79–83.
80. Forsythe P, Ebeling C, Gordon JR, Befus AD, Vliagoftis H. Opposing effects of short- and long-term stress on airway inflammation. Am J Respir Crit Care Med. 2004;169(2):220–6.
81. Joachim RA, Quarcoo D, Arck PC, Herz U, Renz H, Klapp BF. Stress enhances airway reactivity and airway inflammation in an animal model of allergic bronchial asthma. Psychosom Med. 2003;65(5):811–5.
82. Joachim RA, Sagach V, Quarcoo D, Dinh QT, Arck PC, Klapp BF. Neurokinin-1 receptor mediates stress-exacerbated allergic airway inflammation and airway hyperresponsiveness in mice. Psychosom Med. 2004;66(4):564–71.
83. Okuyama K, Ohwada K, Sakurada S, Sato N, Sora I, Tamura G, et al. The distinctive effects of acute and chronic psychological stress on airway inflammation in a murine model of allergic asthma. Allergol Int. 2007;56(1):29–35.
84. Alkon A, Lippert S, Vujan N, Rodriguez ME, Boyce WT, Eskenazi B. The ontogeny of autonomic measures in 6- and 12-month-old infants. Dev Psychobiol. 2006;48(3):197–208.
85. McFadden ERJ, Luparello T, Lyons HA, Bleecker ER. The mechanism of action of suggestion in the induction of acute asthma attacks. Psychosom Med. 1969;31:134–43.
86. Neild JE, Cameron IR. Bronchoconstriction in response to suggestion: its prevention by an inhaled anticholinergic agent. Br Med J. 1985;290:674.
87. Ritz T, Kullowatz A. Effects of stress and emotion on lung function in health and asthma. Curr Respir Med Rev. 2005;1:208–19.
88. Kullowatz A, Smith H-J, Weber S, Kannie F, Mangnussen H, Dahme B, et al. The role of the cholinergic pathway in airway response to emotional stimuli. Psychophysiology. 2007;44:S71.
89. Ritz T, Thoens M, Dahme B. Modulation of respiratory sinus arrhythmia by respiration rate and volume: stability across postures and volume variations. Psychophysiology. 2001;38:858–62.
90. Ritz T, Thoens M, Fahrenkrug S, Dahme B. The airways, respiration, and respiratory sinus arrhythmia during picture viewing. Psychophysiology. 2005;42:568–78.
91. Suglia SF, Staudenmayer J, Cohen S, Bosquet Enlow M, Rich-Edwards JW, Wright RJ. Cumulative stress and cortisol disruption among Black and Hispanic pregnant women in an urban cohort. Psychol Trauma. 2010;2:326–34.
92. Bosquet-Enlow M, Kullowatz A, Staudenmayer J, Spasojevic J, Ritz T, Wright RJ. Associations of maternal lifetime trauma and perinatal traumatic stress symptoms with infant cardiorespiratory reactivity to psychological challenge. Psychosom Med. 2009;71:607–14.

93. Prakash YS, Thompson MA, Meuchel L, Pabelick CM, Mantilla CB, Zaisi S, et al. Neurotrophins in lung health and disease. Exp Rev Respir Med. 2010;4(3):395–411.
94. Gomariz RP, Juarranz Y, Abad C, Arranz A, Leceta J, Martinez C. VIP-PACAP system in immunity: new insights for multitarget therapy. Ann N Y Acad Sci. 2006;1070:51–74.
95. Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S, Senba E. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. Neurosci Res. 1997;28:103–10.
96. Hashimoto H, Shintani N, Tanida M, Hayata A, Hashimoto R, Baba A. PACAP is implicated in the stress axes. Curr Pharm Des. 2011;17:985–9.
97. Joachim RA, Noga O, Sagach V, Hanf G, Fliege H, Kocalevent RD, et al. Correlation between immune and neuronal parameters and stress perception in allergic asthmatics. Clin Exp Allergy. 2008;38(2):283–90.
98. Schulte-Herbruggen O, Nassenstein C, Lommatzsch M, Quarcoo D, Renz H, Braun A. Tumor necrosis factor-[alpha] and interleukin-6 regulate secretion of brain-derived neurotrophic factor in human monocytes. J Neuroimmunol. 2005;160:204–9.
99. Joachim RA, Cifuentes LB, Sagach V, Quarcoo D, Hagen E, Arck PC, et al. Stress induces substance P in vagal sensory neurons innervating the mouse airways. Clin Exp Allergy. 2006;36(8):1001–10.
100. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol. 2002;21(6):531–41.
101. Haczku A, Panettieri RA. Social stress and asthma: the role of corticosteroid insensitivity. J Allergy Clin Immunol. 2010;125:550–8.
102. Wright RJ. Stress and atopic disorders. J Allergy Clin Immunol. 2005;116(6):1301–6.
103. Marwick JA, Wallis G, Meja K, Kuster B, Bouwmeester T, Chakravarty P, et al. Oxidative stress modulates theophylline effects on steroid responsiveness. Biochem Biophys Res Commun. 2008;377(3):797–802.
104. Adcock IM, Barnes PJ. Molecular mechanisms of corticosteroid resistance. Chest. 2008;134:394–401.
105. Wenzel SE, Schwartz LB, Langmack EL, Haliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999;160(3):1001–8.
106. Bush A. How early do airway inflammation and remodeling occur? Allerol Int. 2008;57:11–9.
107. Ito K, Herbert C, Diegle JS, Vuppusetty C, Hansbro N, Thomas PS, et al. Steroid-resistant neutrophilic inflammation in a mouse model of an acute exacerbation of asthma. Am J Respir Cell Mol Biol. 2008;39:543–50.
108. Miller GE, Gaudin A, Zysk E, Chen E. Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity. J Allergy Clin Immunol. 2009;123:824–30.
109. Corwin EJ, Guo Y, Pajer K, Lowe N, McCarthy D, Schmiege S, et al. Immune dysregulation and glucocorticoid resistance in minority and low income pregnant women. Psychoneuroendocrinology. 2013;38(9):1786–96.
110. Vanhees K, van Schooten FJ, van Waalwijk van Doorn-Khosrovani SB, van Helden S, Munnia A, Peluso M, et al. Intrauterine exposure to flavonoids modifies antioxidant status at adulthood and decreases oxidative stress-induced DNA damage. Free Radic Biol Med. 2013;57:154–61.
111. Wainstock T, Shoham-Vardi I, Glasser S, Anteby E, Lerner-Geva L. Fetal sex modifies effects of prenatal stress exposure and adverse birth outcomes. Stress. 2015;18:49–56.
112. Khashan AS, Everard C, McCowan LM, Dekker G, Moss-Morris R, Baker PN, et al. Second-trimester maternal distress increases the risk of small for gestational age. Psychol Med. 2014;44(13):2799–810.
113. Amugongo SK, Hlusko LJ. Impact of maternal prenatal stress on growth of the offspring. Aging Dis. 2014;5(1):1–16.

114. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, et al. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis. 1992;145(5):1129–35.
115. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. Am J Respir Crit Care Med. 1999;159(2):403–10.
116. Chan SW, Chevalier S, Aprikian A, Chen JZ. Simultaneous quantification of mitochondrial DNA damage and copy number in circulating blood: a sensitive approach to systemic oxidative stress. BioMed Res Int. 2013;2013:157547.
117. Sinha K, Das J, Pal PB, Sil PC. Oxidative stress: the mitochondria-dependent and mitochondria-independent pathways of apoptosis. Arch Toxicol. 2013;87(7):1157–80.
118. Lee HC, Wei YH. Mitochondrial role in life and death of the cell. J Biomed Sci. 2000;7(1):2–15.
119. Harrison CM, Pompilius M, Pinkerton KE, Ballinger SW. Mitochondrial oxidative stress significantly influences atherogenic risk and cytokine-induced oxidant production. Environ Health Perspect. 2011;119(5):676–81.
120. Girodet PO, Ozier A, Bara A, Tunon de Lara JM, Marthan R, Berger P. Airway remodeling in asthma: new mechanisms and potential for pharmacological intervention. Pharmacol Ther. 2011;120:325–37.
121. Djuric Z, Bird CE, Furumoto-Dawson A, Rauscher GH, Ruffin MT, Stowe RP, et al. Biomarkers of psychological stress in health disparities research. Open Biomarkers J. 2008;1:7–19.
122. Raby BA, Klanderman B, Murphy A, Mazza S, Camargo CAJ, Silverman EK, et al. A common mitochondrial haplogroup is associated with elevated total serum IgE levels. J Allergy Clin Immunol. 2007;120:351–8.
123. Meert KL, McCaulley L, Sarnaik AP. Mechanism of lactic acidosis in children with acute severe asthma. Pediatr Crit Care Med. 2012;13(1):28–31.
124. Ostroukhova M, Goplen N, Karim MZ, Michalec L, Guo L, Liang Q, et al. The role of low-level lactate production in airway inflammation in asthma. Am J Physiol Lung Cell Mol Physiol. 2012;302:L300–7.
125. Aravamudan B, Thompson MA, Pabelick CM, Prakash YS. Mitochondria in lung diseases. Expert Rev Respir Med. 2013;7(6):631–46.
126. Haas RH, Parikh SM, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease: a practical approach for primary care physicians. Pediatrics. 2007;120(6):1326–33.
127. Chodaczek G, Bacsi A, Dharajiya N, Sur S, Hazra TK, Boldogh I. Ragweed pollen-mediated IgE-independent release of biogenic amines from mast cells via induction of mitochondrial dysfunction. Mol Immunol. 2009;46:2505–14.
128. Moller M, Du Preez JL, Viljoen FP, Berk M, Emsley R, Harvey BH. Social isolation rearing induces mitochondrial, immunological, neurochemical and behavioural deficits in rats, and is reversed by clozapine or N-acetyl cysteine. Brain Behav Immun. 2013;30:156–67.
129. Hendricks S, Ojuka E, Kellaway LA, Mabandla MV, Russell VA. Effect of maternal separation on mitochondrial function and role of exercise in a rat model of Parkinson's disease. Metab Brain Dis. 2012;27(3):387–92.
130. Janicki-Deverts D, Cohen S, Matthews KA, Gross MD, Jacobs Jr DR. Socioeconomic status, antioxidant micronutrients, and correlates of oxidative damage: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Psychosom Med. 2009;71(5):541–8.
131. Feairheller DL, Park JY, Sturgeon KM, Williamson ST, Diaz KM, Veerabhadrappa P, et al. Racial differences in oxidative stress and inflammation: in vitro and in vivo. Clin Transl Sci. 2011;4(1):32–7.
132. Watters JL, Satia JA, Kupper LL. Correlates of antioxidant nutrients and oxidative DNA damage differ by race in a cross-sectional study of healthy African American and white adults. Nutr Res. 2008;28(9):565–76.
133. Wust S, Van Rossum EF, Federenko IS, Koper JW, Kumsta R, Hellhammer DH. Common polymorphisms in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. J Clin Endocrinol Metab. 2004;89(2):565–73.

134. Yamada Y, Nakamura H, Adachi T, Sannohe S, Oyamada H, Kayaba H, et al. Elevated serum levels of thioredoxin in patients with acute exacerbation of asthma. Immunol Lett. 2003;86(2):199–205.
135. Uhart M, McCaul ME, Oswald LM, Choi L, Wand GS. GABRA6 gene polymorphism and an attenuated stress response. Mol Psychiatry. 2004;9:998–1006.
136. Jeanmonod P, von Kanel R, Maly FE, Fischer JE. Elevated plasma C-reactive protein in chronically distressed subjects who carry the A allele of the TNF-alpha -308 G/A polymorphism. Psychosom Med. 2004;66(4):501–6.
137. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. 2003;35:245–54.
138. Miller RL, Ho SM. Environmental epigenetics and asthma: current concepts and call for studies. Am J Respir Crit Care Med. 2008;177(6):567–73.
139. Prescott SL, Clifton V. Asthma and pregnancy: emerging evidence of epigenetic interactions in utero. Curr Opin Allergy Clin Immunol. 2009;9:417–26.
140. Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. Nature. 2007;447(7143):433–40.
141. Castro M, Ramirez MI, Gern JE, Cutting G, Redding G, Hagood JS, et al. Strategic plan for pediatric respiratory diseases research: an NHLBI working group report. Proc Am Thorac Soc. 2009;15:1–10.
142. Levenson JM, Sweatt JD. Epigenetic mechanisms: a common theme in vertebrate and invertebrate memory formation. Cell Mol Life Sci. 2006;63(9):1009–16.
143. Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenal axis in humans. Psychol Bull. 2007;133(1):25–45.
144. Meaney MJ, Szyf M. Maternal care as a model for experience-dependent chromatin plasticity? Trends Neurosci. 2005;28(9):456–63.
145. Szyf M, McGowan P, Meaney MJ. The social environment and the epigenome. Environ Mol Mutagen. 2008;49(1):46–60.
146. Wright R, Bosquet EM. Maternal stress and perinatal programming in the expression of atopy. Expert Rev Clin Immunol. 2008;4:535–8.
147. Turner JD, Pelascini LP, Macedo JA, Muller CP. Highly individual methylation patterns of alternative glucocorticoid receptor promoters suggest individualized epigenetic regulatory mechanisms. Nucleic Acids Res. 2008;36:7207–18.
148. Krozowski ZS, Provencher PH, Smith RE, Obeyesekere VR, Mercer WR, Albiston AL. Isozymes of 11 beta-hydroxysteroid dehydrogenase: which enzyme endows mineralocorticoid specificity? Steroids. 1994;59:116–20.
149. Esposito E, Cuzzocrea S. The role of nitric oxide synthases in lung inflammation. Curr Opin Investig Drugs. 2007;8:899–909.
150. Danson EJ, Li D, Wang I, Dawson TA, Paterson DJ. Targeting cardiac sympatho-vagal imbalance using gene transfer of nitric oxide synthase. J Mol Cell Cardiol. 2009;46:482–9.
151. McLeod TM, Lopez-Figueroa AL, Lopez-Figueroa MO. Nitric oxide, stress, and depression. Psychopharmacol Bull. 2001;35:24–41.
152. Tarantini L, Bonzini M, Apostoli P, Pegoraro V, Bollati V, Marinelli B, et al. Effects of particulate matter on genomic DNA methylation content and iNOS promoter methylation. Environ Health Perspect. 2009;117(2):217–22.
153. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. J Clin Investig. 2004;114:1146–57.
154. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nat Neurosci. 2004;7:847–54.
155. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associated with childhood abuse. Nat Neurosci. 2009;12:342–8.
156. McGowan PO, Suderman M, Sasaki A, Huang TC, Hallett M, Meaney MJ, et al. Broad epigenetic signature of maternal care in the brain of adult rats. PLoS One. 2011;6(2), e14739.

157. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics. 2008;3:97–106.
158. Prakash YS, Martin RJ. Brain-derived neurotrophic factor in the airways. Pharmacol Ther. 2014;143:74–86.
159. Keet CA, McCormack MC, Pollack CE, Peng RD, McGowan E, Matsui EC. Neighborhood poverty, urban residence, race/ethnicity, and asthma: rethinking the inner-city asthma epidemic. J Allergy Clin Immunol. 2015;135:655–62.
160. Oraka E, Iqbal S, Flanders WD, Brinker K, Garbe P. Racial and ethnic disparities in current asthma and emergency department visits: findings from the National Health Interview Survey, 2001-2010. J Asthma. 2013;50(5):488–96.
161. Ortega H, Prazma C, Suruki RY, Li H, Anderson WH. Association of CHI3L1 in African-Americans with prior history of asthma exacerbations and stress. J Asthma. 2013;50(1):7–13.
162. Theoharides TC, Enakuaa S, Sismanopoulos N, Asadi S, Papadimas EC, Angelidou A, et al. Contribution of stress to asthma worsening through mast cell activation. Ann Allergy Asthma Immunol. 2012;109(1):14–9.
163. Trueba AF, Ritz T. Stress, asthma, and respiratory infections: pathways involving airway immunology and microbial endocrinology. Brain Behav Immun. 2013;29:11–27.
164. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun. 2007;21(8):993–9.
165. Bacon SL, Bouchard A, Loucks EB, Lavoie KL. Individual-level socioeconomic status is associated with worse asthma morbidity in patients with asthma. Respir Res. 2009;10:125.
166. Ungar WJ, Paterson JM, Gomes T, Bikangaga P, Gold M, To T, et al. Relationship of asthma management, socioeconomic status, and medication insurance characteristics to exacerbation frequency in children with asthma. Ann Allergy Asthma Immunol. 2011;106(1):17–23.
167. Braveman P, Marchi K, Egerter S, Kim S, Metzler M, Stancil T, et al. Poverty, near-poverty, and hardship around the time of pregnancy. Matern Child Health J. 2010;14:20–35 [Epub ahead of print].
168. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CR. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52:1048–60.
169. Holman EA, Silver RC, Waitzkin H. Traumatic life events in primary care patients: a study in an ethnically diverse sample. Arch Fam Med. 2000;9(9):802–10.
170. Hien D, Bukszpan C. Interpersonal violence in a “normal” low-income control group. Women Health. 1999;29(4):1–16.
171. Clark C, Ryan L, Kawachi I, Jacobson Canner M, Berkman LF, Wright RJ. Witnessing community violence in residential neighborhoods: a mental health hazard for urban women. J Urban Health. 2007;85(1):22–38.
172. Brown JR, Hill HM, Lambert SF. Traumatic stress symptoms in women exposed to community and partner violence. J Interpers Violence. 2005;20:1478–94.
173. Suglia SF, Ryan L, Laden F, Dockery DW, Wright RJ. Violence exposure, a chronic psychosocial stressor, and childhood lung function. Psychosom Med. 2008;70(2):160–9.
174. Stokols D. Establishing and maintaining healthy environments: toward a social ecology of health promotion. Am Psychol. 1992;47:6–22.
175. Francis DD. Conceptualizing child health disparities: a role for developmental neurogenomics. Pediatrics. 2009;124:S196–202.
176. Wright RJ, Subramanian SV. Advancing a multilevel framework for epidemiological research on asthma disparities. Chest. 2007;132:757S–69.
177. Evans G. Environmental stress and health. In: Baum A, Revenson T, Singer J, editors. Handbook of health psychology. Mahwah: Lawrence Erlbaum; 2001. p. 365–85.
178. Sternthal MJ, Bosquet Enlow M, Cohen S, Jacobson Canner M, Staudenmayer J, Tsang K, et al. Maternal interpersonal trauma and cord blood IgE levels in an inner-city cohort: a life-course perspective. J Allergy Clin Immunol. 2009;124:954–60.

179. Sternthal MJ, Jun HJ, Earls F, Wright RJ. Community violence and urban childhood asthma: a multilevel analysis. Eur Respir J. 2010;36(6):1400–9.
180. Chiu YH, Coull BA, Sternthal MJ, Kloog I, Schwartz J, Cohen S, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. J Allergy Clin Immunol. 2014;133(3):713–22.e4.
181. Apter AJ, Garcia LA, Boyd RC, Wang X, Bogen DK, Ten Have T. Exposure to community violence is associated with asthma hospitalizations and emergency department visits. J Allergy Clin Immunol. 2010;126(3):552–7.
182. Sandel M, Wright RJ. Expanding dimensions of housing that influence asthma morbidity: when home is where the stress is. Arch Dis Child. 2006;91:942–8.
183. Quinn K, Kaufman JS, Siddiqi A, Yeatts KB. Stress and the city: housing stressors are associated with respiratory health among low socioeconomic status Chicago children. J Urban Health. 2010;87:688–702 [Epub ahead of print].
184. Suglia SF, Duarte CS, Sandel MT, Wright RJ. Social and environmental stressors in the home and childhood asthma. J Epidemiol Community Health. 2010;64(7):636–42.
185. Jacobs DE, Ahonen E, Dixon SL, Dorevitch S, Breysse J, Smith J, et al. Moving into green healthy housing. J Public Health Manag Pract. 2014;21:345–54.
186. Mrazek DA, Klinnert M, Mrazek PJ, Brower A, McCormick D, Rubin B, et al. Prediction of early-onset asthma in genetically at-risk children. Pediatr Pulmonol. 1999;27(2):85–94.
187. Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. Am J Respir Crit Care Med. 2002;165:358–65.
188. Suglia SF, Enlow MB, Kullowatz A, Wright RJ. Maternal intimate partner violence and increased asthma incidence in children: buffering effects of supportive caregiving. Arch Pediatr Adolesc Med. 2009;163(3):244–50.
189. Clougherty J, Levy JI, Kubzansky LD, Ryan B, Franco Suglia S, Jacobson Canner M, et al. The effects of traffic-related air pollution and exposure to violence on urban asthma etiology. Environ Health Perspect. 2007;115(8):1140–6.
190. Chen E, Schreier HM, Strunk RC, Brauer M. Chronic traffic-related air pollution and stress interact to predict biologic and clinical outcomes in asthma. Environ Health Perspect. 2008;116:970–5.
191. Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. Proc Natl Acad Sci U S A. 2009;106:12406–11.

Chapter 9
Health Disparities in Asthma

Christian Bime

Key Points

- Children, women, racial and ethnic minorities, residents of inner cities, and economically disadvantaged populations have a significantly higher burden of asthma.
- Health disparities in asthma result from a complex interaction of multiple factors including: patient-related factors, factors related to the health care system, as well as social and environmental factors.
- Future research on asthma health disparities should involve a multidisciplinary and simultaneous examination of the complex interactions between the individual, socioeconomic, cultural, and health system factors involved.

Introduction

When compared to the general population or other populations, children, women, racial and ethnic minorities, residents of inner cities, and economically disadvantaged populations in the United States have a significantly higher burden of asthma [1–4]. Children in the United States have twice the self-reported asthma attack prevalence rates and two to three times the annual rate of emergency department (ED) visits for asthma than adults [2, 4]. Among adults, women have twice the annual rate of ED visits for asthma when compared to men [4]. In terms of disparities by geographic location, several studies from three decades ago in large US cities such

C. Bime, M.D., M.Sc. (✉)
Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, College of Medicine, University of Arizona, 1501 N. Campbell Ave, 245030A, Tucson, AZ 85724, USA
e-mail: cbime@email.arizona.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_9

as Boston, Chicago, Los Angeles, and New York City, revealed significantly asthma morbidity and mortality in inner-city neighborhoods compared to suburban areas [5–8]. Residents of inner-city neighborhoods are also more likely to be of low socioeconomic status (SES) and have poor access to care [8, 9]. Racial and ethnic minority populations also have a high burden of asthma [10]. For the purposes of this chapter, race will refer to white, Black or African American, Asian, Hawaiian or other Pacific Islander, and American Indian or Alaska native. Ethnicity will refer to Hispanic or Latino and not Hispanic or Latino. In the United States, data shows that compared to non-Hispanic whites, racial and ethnic minority populations have significantly higher morbidity andmortality from asthma [2, 4]. Economically disadvantaged populations, many of whom are from racial/ethnic minority groups, and predominantly reside in inner-city neighborhoods have a significantly higher burden of asthma [8]. According to the Expert Panel Report 3 (EPR3) guidelines on asthma published by National Heart, Lung, and Blood Institute (NHLBI) in 2007, ethnic and racial disparities in asthma burden are a persisting problem—with significant negative impact on African American and Puerto Rican populations—despite overall improvements in mortality from asthma [11].

Health disparities in asthma probably result from a complex interaction of multiple factors including: patient-related factors, factors related to the health care system, as well as social and environmental factors [12, 13]. The burden of asthma health disparities necessitates an increase in resources directed to studying the mechanisms that lead to and sustain asthma health disparities [14, 15]. The CDC *Health Disparities and Inequalities Report—United States*, *2011* includes a detailed report of prevailing asthma disparities in the US population [2, 16]. It also offers recommendations for addressing health disparities in asthma [16]. The ultimate goal is to develop evidence-based strategies for addressing issues of asthma health disparities.

In this chapter, we will review the epidemiology of asthma in the USA, with a special focus on the burden of asthma among children, women, racial/ethnic minorities, and economically disadvantaged populations, who are disproportionately negatively affected. We will then explore the factors associated with asthma health disparities in the USA. Next, we will discuss a conceptual model that has been proposed to explain the interaction of various factors associated with asthma health disparities. Currently proposed strategies for addressing asthma health disparities will be then reviewed. Finally, a summary of federal programs directed at addressing asthma health disparities will be presented.

Asthma Overview

Asthma is a common chronic inflammatory disorder of the airways, characterized by episodic and reversible airflow obstruction, airway hyperresponsiveness, and underlying inflammation [11]. These features interact to determine the clinical syndrome of asthma which includes one or more of the following clinical manifestations: recurrent wheezing, coughing—especially at night, shortness of breath, chest

tightness, and exercise limitation [11]. Intermittent episodes of increased asthma symptoms—asthma attacks—typically occur after exposure to specific asthma triggers such as viral respiratory infections, mold, pollen, dust mites, cockroach allergen, tobacco smoke, outdoor air pollution, strong odors and fumes, exercise and physical exertion, cold air, stress, etc.

The hallmark of asthma is a variable and reversible airflow obstruction—secondary to bronchoconstriction [11]. Reversibility can occur spontaneously or in response to treatment with bronchodilators [11]. A diagnosis of asthma is usually suggested by the characteristics and pattern of typical asthma symptoms, especially in association with known exposure or sensitization to specific asthma triggers. Evidence of significant reversibility of airflow obstruction with bronchodilators, or significant hyperresponsiveness to airway constrictor agents such as methacholine, or a positive response to appropriate asthma therapy confirms the diagnosis of asthma [11]. The management of asthma is multifaceted and aims to reduce the risk of asthma morbidity, functional impairment related to asthma, and mortality [11]. The main tenets of management include trigger reduction and avoidance, assessing level of asthma control, medication therapy, and monitoring level of disease activity [11]. In many asthma patients, current treatment strategies are effective in controlling symptoms. Unfortunately, no therapy has been shown to significantly alter the natural course of asthma. This is likely due to our limited understanding of the natural history of asthma.

Several studies, including cohort studies in the U.S. have examined the natural history of asthma from birth, through adolescence to young adulthood [17, 18]. Distinct early childhood wheezing phenotypes as well as risk factors for persistent wheezing and subsequent asthma diagnosis have been identified [19]. The inherent heterogeneity of the asthma phenotype, variable response to asthma therapy, and the different temporal trajectories that asthma patients follow from early childhood through adulthood complicate our current understanding of the natural history of asthma. Few cohorts have studied the natural history of adult asthma [20–22]. A variety of studies, using both biased (hypothesis-based) approaches or unbiased (statistical-based) approaches have identified distinct phenotypes of asthma in adults including early onset allergic asthma, late-onset eosinophilic asthma, exercise-induced asthma, obesity-related asthma, and neutrophilic asthma [23–27]. It should be noted that the number and features of subphenotypes identified in these studies are limited by the study population and the choice of variables included in the analysis, regardless of the approach used.

Asthma Disparities in the United States

Disparities in Asthma Prevalence

Differences exist in asthma prevalence by age group, gender, race, SES, and geographic region in the United States [2]. According to surveillance data for the period 2008–2010, the average annual current asthma prevalence was higher in children

than adults (9.5 % versus 7.7 %), higher in females than in males (9.2 % versus 7.0 %), higher in blacks than in whites (11.2 % versus 7.7 %), higher among Hispanics with roots in Puerto Rico versus Hispanics with roots in Mexico (16.1 % versus 5.4 %), higher among persons with family income below 100 % of federal poverty threshold versus those with family income at or above the federal poverty threshold (11.2 % versus 8.5 %) [10]. In terms of geographic region, the current asthma prevalence rate was higher in the Northeast and Midwest than in the South (8.8 % versus 7.6 %) [10]. In the West, the reported asthma prevalence rate was 8.0 % [10]. Interestingly, there was no difference between metropolitan and nonmetropolitan areas in terms of current asthma prevalence [10]. Previous reports have reported similar racial differences in asthma prevalence [28–30]. In a 1987 report of U.S. asthma surveillance data for the period from 1965 to 1984, significant differences in asthma prevalence rates, emergency department visit rates, and hospitalization rates by race/ethnicity were reported [30]. Other reports from the Centers for Disease Control and Prevention (CDC) have generally confirmed these significant racial and ethnic disparities in asthma morbidity and mortality [2, 15, 16]. In 2011, the CDC analyzed data from the National Health Interview Survey (NHIS) for the period 2006–2008 and reported both lifetime asthma prevalence and current prevalence of asthma by various demographic subgroups [2, 16]. According to the 2011 CDC Health Disparities and Inequalities Report (CHDIR), the estimated current prevalence of asthma of the U.S. population was 7.8 % with significant variation by racial or ethnic group. Current asthma prevalence was 15.9 % among Puerto Ricans, 14.4 % among multiracial/other-race persons, 10.5 % among blacks, 10.8 % among American Indians/Alaska Natives, 7.9 % among whites, and 5.4 % among Mexicans [2, 12]. In that report, current asthma prevalence also varied by age, gender, and SES. Current asthma prevalence was higher among children (9.3 %) than among adults (7.3 %). It was also higher among females (8.6 %) than among males (6.9 %), and among those considered poor (11.2 %) than those considered nonpoor (7 %). Among children (0–17 years of age) the racial/ethnic disparities in current asthma prevalence were even greater. The current asthma prevalence was 18.4 % among Hispanic children with roots in Puerto Rico, 14.6 % among non-Hispanic blacks, 13.6 % among multiracial children, and 8.2 % among non-Hispanic whites [2, 12]. Among adults, there was no difference in current asthma prevalence between non-Hispanic blacks (7.8 %) and non-Hispanic whites (7.7 %) [2, 12]. However, the current asthma prevalence was disproportionately higher among multiracial persons (15.1 %) and Hispanics with roots in Puerto Rico (12.8 %). An important finding is that the current asthma prevalence for Hispanics of Puerto Rican ancestry (14.2 %) is much higher than Hispanics of Mexican ancestry (4.9 %) [2, 12].

Disparities in Asthma Morbidity

The 2013 CHDIR report is based on data from the 2001–2010 NHIS survey and provides information about asthma attacks among persons with current asthma [4, 12, 14, 15]. The definition of asthma attacks was based on an affirmative response

to the following survey question—"During the past 12 months, have you had an episode of asthma or an asthma attack?" Some notable differences between the periods 2001–2004 and 2006–2010 exist in terms of proportion of reported attacks in the past year. In general, the period 2001–2004 had a slightly higher percentage of persons with current asthma who reported an asthma attack in the past year compared to the period 2006–2010. Overall, during the period from 2006 to 2010, asthma attacks were reported more frequently for females (53.5 %) than for males (48.8 %), and more frequently for children (56.1 %) than for adults (49.6 %) [4, 12]. In terms of differences by geographic region, even though the current prevalence of asthma was higher in the Northeast and Midwest than in the South and West, more asthma attacks were reported in the South (53.1 %) and West (54.5 %) compared to the Northeast (47.8 %) and the Midwest (49.4 %) [4, 10]. The survey assessed frequency of asthma attacks by level of education and did not find any significant differences between those with less than a high school education (51.2 %) and those with college or graduate education (52.1 %) [4, 31]. In terms of race or ethnicity, asthma attacks were reported more frequently among patients who self-identified as American Indian/Alaska Native (61.6 %) than among non-Hispanic whites (51.1 %), blacks (49.1 %), Hispanics with roots in Mexico (52.6 %), and Hispanics with roots in Puerto Rico (55.6 %) [4, 12]. It should be noted that only 92 (0.6 %) of the 14,230 patients sampled were American Indian/Alaska native [4, 12].

Significant differences in rate of ED visits for asthma by age, gender, and race or ethnicity were reported from the U.S. National Hospital Ambulatory Medical Care Survey (NHAMCS) for the period 2005–2007 [1, 4, 12]. Overall, children, especially those less than 5 years old, are more susceptible to asthma attacks requiring ED visits. Among children less than 5 years old, the annual rates of ED visits for asthma were higher when compared to children 5–17 years old (133/10,000 versus 73/10,000). Among adults, the annual rates of ED visits for asthma were lower than among children (47/10,000 versus 133/10,000 and 73/10,000 for children less than 5 years old and those 5–17 years old, respectively) [4]. Gender differences in annual rates of ED visits differed by age group [4]. Among children less than 5 years old, the annual rate of ED visits was higher for males than females (170.5/10,000 versus 94.1/10,000). Among adults, the annual rate of ED visits was higher for female than males (61.5/10,000 versus 32.7/10,000). For those 5–17 years old, there was no difference in annual rates of ED visits by gender (74.5/10,000 and 71.9/10,000 for males and females, respectively) [4]. In terms of race and ethnicity, the annual rates of emergency department visits for blacks (167/10,000) were significantly higher compared to whites (42.5/10,000) [4, 12]. Among Hispanics, the rates were 64.8/10,000. The data on Hispanics does not differentiate between the different subgroups of Hispanics.

According to the 2004 National Hospital Discharge Survey, the estimated rate of hospital discharges with asthma listed as the first diagnosis was significantly higher for blacks (33.5/10,000) than for whites (10/10,000) or other races (19/10,000) [12, 32]. The U.S. NHAMCS does not include information on metropolitan versus nonmetropolitan residences or SES. However, previous studies in the 1990s showed that hospitalization for asthma was more common among patients from poor inner-city neighborhoods compared to those from more affluent suburban neighborhoods [5–7].

Disparities in Asthma Mortality

Several studies in the 1980s and 1990s showed in several US metropolitan areas, mortality from asthma was significantly higher in inner-city neighborhoods compared to suburban areas [5, 7–9, 33, 34]. Inner-city populations tend to be of low SES, be racial or ethnic minorities, have poor access to care, be more exposed to environmental pollutants, and live in crowded conditions leading to increased exposure to allergens and infections [9, 33]. This higher mortality is likely due to a complex interaction of multiple factors that are characteristic of life in large urban poor neighborhoods. In terms of racial or ethnic differences in asthma mortality, data from the National Vital Statistics System (NVSS) for the period 1990–2007 showed a significantly higher mortality due to asthma for blacks compared to whites, especially among children ages 0–17 years old [4, 12, 35]. Among children ages 0–17 years old, the annual rate of deaths with asthma as the underlying cause of death among blacks was 0.8/100,000 compared to 0.1/100,000 among whites and 0.2/100,000 among Hispanics. Among adults older than 18 years, there is also a significant difference between blacks and other races in terms of the annual rate of deaths with asthma as the underlying diagnosis. However, it should be noted that there has been a trend toward a decrease in asthma-related mortality among blacks from 4.8 deaths per 100,000 in 1999–2001 to 3.4/100,000 in 2005–2007 [12]. Comparatively, among whites older than 18 years old, the annual rate of deaths due to asthma was 1.2/100,000 [12].

In summary, U.S. surveillance data as reported by the CDC reveals significant disparities in the prevalence, morbidity, and mortality related to asthma. Children, women, economically disadvantaged persons, and certain racial or ethnic groups (Africa-Americans, Puerto Ricans, multiracial persons, and American Indian/Alaska Natives) are disproportionately negatively impacted by asthma in terms of prevalence, urgent care and emergency department visits, hospitalizations, and fatalities due to asthma when compared to non-Hispanic whites. The prevalence of asthma among African Americans is about 40 % higher than in non-Hispanic white Americans [12]. The mortality from asthma among African Americans is twice that of non-Hispanic whites [12]. Puerto Ricans have a higher asthma prevalence and mortality than African Americans [12]. Mexican Americans have lower asthma prevalence, morbidity, and mortality than non-Hispanic whites, African Americans, and Puerto Ricans [12]. The possible explanations for these racial/ethnic disparities in asthma are multifactorial, complex, and poorly understood. This is an active area of research. In the next section, we will explore the associations between putative factors and racial/ethnic disparities in asthma.

Factors Associated with Asthma Health Disparities

Many factors contribute to the observed health disparities in asthma [12, 13]. The relative impact of each factor is difficult to quantify. It is more likely that a complex interaction of several factors contributes to observed disparities in asthma

prevalence, morbidity, and mortality [13]. Studying the factors associated with asthma disparities involves a multidisciplinary approach involving various stakeholders including: patients or community advocates from racial or ethnic minority populations, health providers including asthma specialists, basic and clinical researchers, social cognitive researchers, health care administrators, and other government administrators. For ease of discussion, the factors associated with health disparities in asthma are classified into the following three categories: patient-related factors, social/environmental factors, and factors-related to health care providers or the health care system [13]. For each of these categories, we discuss available evidence of an association with differences in prevalence, severity, and mortality of asthma. We also discuss how these factors might interact with each other to increase the disparities.

Patient-Related Factors

There is evidence that genetic factors might play a role in racial/ethnic differences in asthma prevalence and severity. The best example is seen among Hispanics in the United States with a significant difference in prevalence, severity, and mortality between Hispanics of Puerto Rican origin and Hispanics of Mexican heritage [12]. This observation is commonly described as the *Hispanic paradox*. Burchard et al. showed that bronchodilator responsiveness was 7.3 % lower in Puerto Ricans compared to Hispanics with roots in Mexican [36]. A subsequent genetic study showed that bronchodilator responsiveness was strongly associated with Arg16Gly genotypes in Puerto Ricans but not in Mexicans [37]. Racial differences in certain physiologic variables between American children of European descent and African American children were reported by Joseph et al. [38]. Compared to a matched cohort of American children of European descent, middle-class African American children with asthma had decreased forced vital capacity (FCV) and forced expiratory volume in 1 s (FEV1) [38]. They also had increased airway hyperresponsiveness and increased total serum immunoglobulins E (IgE) levels [38]. Compared to non-Hispanic whites, Puerto Rican and African American children were noted to be significantly more likely to be allergic to several outdoor allergens [39]. Genome-wide association studies (GWASs) have confirmed the important contribution of genetic component to asthma but do not fully explain the observed racial or ethnic disparities [40, 41]. Even though racial or ethnic variability in the distribution of some genetic polymorphisms might determine susceptibility to asthma, this is not sufficient to explain observed ethnic differences in asthma observed in the United States [42]. The asthma phenotype is a complex trait that is determined by multiple genes contributing small effects, by gene–gene interactions and by the complex interactions between the genes and numerous environmental factors [42, 43]. The natural history and the pathobiology of asthma are poorly understood. An important concept in the pathobiology of asthma is the hygiene hypothesis which posits that a reduction in endotoxin exposure or microbial load in early life might alter the balance of the immune system in favor of the more active T-helper type 2 responses

that are involved in asthma and allergy [44, 45]. However, the hygiene hypothesis does not explain the high prevalence and morbidity of asthma seen in inner-city African Americans. After all, inner-city African American children do not necessarily experience fewer infections than children from other demographic groups in the United States.

It has been argued that the widening disparities in the prevalence and severity of asthma over the past 3 decades are too rapid to be explained by changes in genetic factors alone [13]. Therefore, other modifiable patient-related behavioral factors likely contribute to these health care disparities. Some families have misconceptions about the susceptibility to asthma [13]. Poor adherence to provider-recommended asthma therapy is another possible factor contributing to high asthma morbidity in minority populations. Common beliefs about the efficacy and safety of medications vary by ethnicity [13]. Minority populations are generally less trusting of standard therapy and are more inclined to try other alternative therapies [46, 47]. A study of 40 parents of children with asthma revealed numerous concerns and barriers to asthma medication use among African American parents [46]. The long-term complications of daily asthma medications use were the most cited concern [46]. There is also evidence of frequent use of home remedies to manage asthma among African Americans and Latinos [47–50]. These attitudes can lead to a delay of appropriate therapy and consequently, more severe disease. Asthma care requires a very active participation from the patient or parent to monitor for changes in control and institute timely interventions. A poor understanding of the disease and lack of awareness about possible complications can contribute to significant disparities in morbidity and mortality of asthma irrespective of prevalence. Racial and ethnic minority populations have a lower health literacy rate than non-Latino whites and might not adequately comply with treatment recommendations of asthma care [51, 52]. An important risk factor for asthma is obesity [53]. The prevalence and severity of obesity among African Americans and Hispanics, especially in poor urban environments is much higher than among non-Hispanic whites and might also contribute to the disparity in asthma burden [54].

Social and Environmental Factors

A concern in interpreting racial and ethnic differences in asthma prevalence, severity, and mortality is the possibility of confounding by SES and other environmental factors [55]. In general, persons with low SES in the United States have poorer health [55–57]. Racial and ethnic minorities are more likely to have a low SES. Compared to non-Hispanic whites, African Americans have higher mortality rates for most illnesses including asthma [55]. They also live in poorer and segregated neighborhoods, mostly in urban areas [55]. These neighborhoods are characterized by higher levels of environmental pollution and stress due to violence. Environmental pollution and stress are well-established risk factors for asthma morbidity and mortality [58]. Indoor allergens such as the cockroach allergen are associated with increased asthma morbidity [59, 60]. Concentrations of the cockroach

allergen are higher in urban homes compared to rural homes. High levels of cockroach allergens are also associated with low SES and African American race [61]. The National Cooperative Inner-City Asthma Study (NCICAS) showed that 85 % of homes had detectable cockroach allergen and 37 % of patients had a positive skin test to cockroach allergen [62, 63]. A combination of high allergen levels in the patient's bedroom and cockroach sensitivity was associated with increased days with wheezing, increased emergency department visits, and increased hospitalizations [62]. Exposure to diesel particles in urban areas is also associated with increased asthma morbidity [64]. Persons with low SES are more likely to reside close to major highways and thus be more exposed to diesel particles [65, 66]. They are also more likely to reside in homes with poor ventilations compared to more affluent suburban residents [59, 67]. Other socioeconomic factors characteristic of life in poor urban neighborhoods and associated with increased asthma morbidity include: poor diet, physical inactivity, obesity, environmental smoke exposure, and depression. Among 4-year-old children, low SES was shown to be a risk factor for asthma [68]. Another study showed that independent of ethnicity and family income, children in low socioeconomic communities had 70 % greater risk of asthma [69]. Saha et al. showed that in a low SES neighborhood, age, race, gender, and body mass index (BMI) were significant predictors of childhood asthma [70].

Patients with low SES also have poor social and/or family function which might impact compliance with treatment recommendations of asthma care. There is an increasing body of evidence linking chronic stress in high-risk neighborhoods and increased asthma exacerbations [58, 71–73]. Chronic stress is associated with increased oxidative stress and this can also lead to an increase in incidence of asthma [71, 72]. Chen et al. showed that children of low SES overexpressed genes that regulated chemokine activity, stress response, and wound healing [74]. On the other hand, children of higher SES overexpressed genes that maybe be involved in containing damage caused by inflammation [74]. It has been suggested that chronic stress and threat perception in low SES neighborhoods might lead to a higher production of markers of eosinophil production and activation. Respiratory syncytial virus (RSV)-induced bronchiolitis in infancy is a risk factor for subsequent development of asthma [75–78]. Studies show that American Indian and Alaska Native infants are significantly more likely to be hospitalized for RSV infections [79, 80]. This might explain the significant asthma disparity in these populations. Children from low SES in inner cities are also more likely to have recurrent hospitalizations for RSV but the current data does not show significant differences between non-Latino whites and other racial or ethnic minorities in inner cities [33].

Factors Related to Health Care System and Health Care Providers

The management of asthma is multifaceted and includes preventive measures such as avoidance and control of relevant triggers, regular use of controller medications, and timely referral to asthma specialists [11]. There is evidence that many health

care providers, especially those who treat racial and ethnic minority populations in inner cities, do not adhere to well-established asthma management guidelines [13]. In one study, pediatricians in practices with more than 25 % of African American children in their practice reported less prescription of daily controller medications (35 %) when compared to pediatricians in all practices (51 %) [13, 81]. It is not clear if limited access to care contributes to observed asthma disparities. Blixen CE et al. showed that African Americans were less likely to have primary care or subspecialty visits for asthma but were more likely to have ED visits for asthma [82]. There are also other important racial and ethnic disparities in medication and healthcare usage for asthma [3]. Analysis of 1485 patients surveyed as part of the National Asthma Survey Database showed that African American and Hispanic children were less likely to have used inhaled corticosteroids (ICS) than white children. They were more likely to receive daily short-acting bronchodilators (SABAs) than white children. Black children had twice as many ED visits and hospitalizations than white children and emergency department visits were positively correlated with SABA use and negatively correlated with ICS use when stratified for race and ethnicity [3]. Compared to non-Hispanic whites, racial and ethnic minority patients in inner cities are more likely to rely on government-sponsored health care plans, such as Medicaid. These health care plans are more tightly regulated for cost control and might limit access to asthma specialists. Overall, there is some suggestion, based on limited available evidence, that minority populations might receive lower quality asthma care, thus contributing to the observed disparities in asthma [12, 13]. Asthma controller medications are expensive and some states have attempted to reduce cost by introducing copayments. Many patients of low SES, especially those of racial and ethnic minority populations have difficulty affording these copayments. The consequence is an increase in frequency of asthma exacerbations and emergency department use for asthma.

It has been suggested that ineffective communication between provider and asthma patients because of racial or ethnic differences might result in misclassification of asthma symptom severity [13]. Such misclassification of asthma severity may lead to undertreatment of asthma and ultimately contribute to the observed racial or ethnic disparities in asthma care. A study of about 3500 asthma patients (13 % black) showed that black patients were significantly more likely than white patients to have their asthma severity underestimated [83]. The study also noted that among the black patients, underestimation of asthma severity was associated with less use of daily ICS, less physician instruction on management of asthma flare-ups, and lower ratings of asthma care and communication [83]. Another suggestion is that unconscious biases against low income and or racial or ethnic minority patients by the provider that might affect the quality of care provided to the patient [13]. A perception that low income and or racial or ethnic minority patients with asthma are noncompliant might affect the quality of care provided. The provider might not take the time to adequately explore the reasons for uncontrolled disease, simply attributing this to noncompliance.

In summary, there is clear evidence of significant disparities in asthma prevalence, morbidity, and mortality in the United States. Asthma disproportionately

negatively affects low-income Americans and especially racial/ethnic minorities such as Puerto Ricans and African Americans. These disparities might very well be genetically based. However, they are also mitigated by socioeconomic, environmental, and cultural factors that limit simplistic explanations. Simply highlighting phenotypic racial differences is a poor surrogate for understanding the interaction between biologic, environmental, and cultural factors that lead to and sustain these disparities in asthma.

Strategies for Addressing Health Disparities in Asthma

The CDC *Health Disparities and Inequalities Report—United States*, *2011* reports recommended certain actions to reduce health disparities in general [2]. These include an increase in community awareness of disparities, setting priorities among the disparities to be addressed, using evidence-based and proven strategies for eliminating health disparities, and a need-based allocation of resources to reduce disparities. Canino et al. have proposed a conceptual model which incorporates a range of risk factors at multiple levels as a first step to understanding and ultimately addressing asthma disparities in the United States [13]. Future research on asthma health disparities should involve a multidisciplinary and simultaneous examination of the complex interactions between individual, socioeconomic, cultural, and health system factors involved. More importantly, adequate representation of members of high-risk populations and minority investigators should be involved in the research. Community-based participatory approaches utilizing community resources should be used. Community-based programs are effective in modifying outcomes because they emphasize engagement, education, and empowerment of the affected populations. An increased focus on validating effective models of education and care that is driven by community stakeholders is therefore needed. In addition to the community approaches, focused research to investigate unique markers that predict disease severity and therapeutic response in racial and ethnic minority populations is needed.

References

1. Moorman JE, Rudd RA, Johnson CA, et al. National surveillance for asthma—United States, 1980-2004. Surveillance summaries. Morb Mort Wkly Rep. 2007;56(8):1–54.
2. Moorman JE, Zahran H, Truman BI, Molla MT. Current asthma prevalence—United States, 2006-2008. Surveillance summaries. Morb Mortal Wkly Rep. 2011;60(Suppl):84–6.
3. Crocker D, Brown C, Moolenaar R, et al. Racial and ethnic disparities in asthma medication usage and health-care utilization: data from the national asthma survey. Chest J. 2009;136(4):1063–71.
4. Moorman JE, Person CJ, Zahran HS. Asthma attacks among persons with current asthma—United States, 2001-2010. Surveillance summaries. Morb Mortal Wkly Rep. 2013;62 Suppl 3:93–8.

5. Gottlieb DJ, Beiser AS, O'Connor GT. Poverty, race, and medication use are correlates of asthma hospitalization rates. A small area analysis in Boston. Chest. 1995;108(1):28–35.
6. Ray NF, Thamer M, Fadillioglu B, Gergen PJ. Race, income, urbanicity, and asthma hospitalization in California: a small area analysis. Chest. 1998;113(5):1277–84.
7. Carr W, Zeitel L, Weiss K. Variations in asthma hospitalizations and deaths in New York City. Am J Public Health. 1992;82(1):59–65.
8. Grant EN, Lyttle CS, Weiss KB. The relation of socioeconomic factors and racial/ethnic differences in US asthma mortality. Am J Public Health. 2000;90(12):1923–5.
9. Marder D, Targonski P, Orris P, Persky V, Addington W. Effect of racial and socioeconomic factors on asthma mortality in Chicago. Chest. 1992;101(6 Suppl):426s–9.
10. Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001-2010. Series 3, Analytical and epidemiological studies/[U.S. Dept. of Health and Human Services, Public Health Service, National Center for Health Statistics]. Vital Health Stat. 2012;(35):1–67.
11. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma–summary report 2007. 2007;120(5 Suppl. 1):S94–138.
12. Leong AB, Ramsey CD, Celedon JC. The challenge of asthma in minority populations. Clin Rev Allergy Immunol. 2012;43(1–2):156–83.
13. Canino G, McQuaid EL, Rand CS. Addressing asthma health disparities: a multilevel challenge. J Allergy Clin Immunol. 2009;123(6):1209–17; quiz 1218–09.
14. Frieden TR. CDC health disparities and inequalities report—United States, 2013. Foreword. Surveillance summaries. Morb Mortal Wkly Rep. 2013;62(Suppl. 3):1–2.
15. Meyer PA, Yoon PW, Kaufmann RB. Introduction: CDC health disparities and inequalities report—United States, 2013. Surveillance summaries. Morb Mortal Wkly Rep. 2013;62(Suppl. 3):3–5.
16. Frieden TR. Forward: CDC health disparities and inequalities report—United States, 2011. Surveillance summaries. Morb Mort Wkly Rep. 2011;60(Suppl.):1–2.
17. Reed CE. The natural history of asthma. J Allergy Clin Immunol. 2006;118(3):543–8; quiz 549–50.
18. Martinez FD. New insights into the natural history of asthma: primary prevention on the horizon. J Allergy Clin Immunol. 2011;128(5):939–45.
19. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. Paediatr Respir Rev. 2004;5(2):155–61.
20. Bonner JR. The epidemiology and natural history of asthma. Clin Chest Med. 1984;5(4):557–65.
21. Slavin RG, Haselkorn T, Lee JH, Zheng B, Deniz Y, Wenzel SE. Asthma in older adults: observations from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. Ann Allergy Asthma Immunol. 2006;96(3):406–14.
22. Sood A, Qualls C, Schuyler M, et al. Adult-onset asthma becomes the dominant phenotype among women by age 40 years. The longitudinal CARDIA study. Ann Am Thorac Soc. 2013;10(3):188–97.
23. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716–25.
24. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181(4):315–23.
25. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218–24.
26. Boudier A, Curjuric I, Basagana X, et al. Ten-year follow-up of cluster-based asthma phenotypes in adults. A pooled analysis of three cohorts. Am J Respir Crit Care Med. 2013;188(5):550–60.
27. Siroux V, Gonzalez JR, Bouzigon E, et al. Genetic heterogeneity of asthma phenotypes identified by a clustering approach. Eur Respir J. 2014;43(2):439–52.

28. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief. 2012;94:1–8.
29. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980-2007. Pediatrics. 2009;123 Suppl 3:S131–45.
30. Akinbami LJ, LaFleur BJ, Schoendorf KC. Racial and income disparities in childhood asthma in the United States. Ambul Pediatr. 2002;2(5):382–7.
31. Mirabelli MC, Beavers SF, Chatterjee AB, Moorman JE. Age at asthma onset and subsequent asthma outcomes among adults with active asthma. Respir Med. 2013;107(12):1829–36.
32. DeFrances CJ, Podgornik MN. National hospital discharge survey. Adv Data. 2004;2006(371):1–19.
33. Weiss KB, Gergen PJ, Crain EF. Inner-city asthma: the epidemiology of an emerging us public health concern. Chest J. 1992;101(6 Suppl):362S–7.
34. Weiss KB, Wagener DK. Geographic variations in US asthma mortality: small-area analyses of excess mortality, 1981-1985. Am J Epidemiol. 1990;132(1 Suppl):S107–15.
35. Akinbami LJ, Sullivan SD, Campbell JD, et al. Asthma outcomes: healthcare utilization and costs. Standardizing asthma outcomes in clinical research: report of the asthma outcomes workshop. J Allergy Clin Immunol. 2012;129(3 Suppl.):S49–64.
36. Burchard EG, Avila PC, Nazario S, et al. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. Am J Respir Crit Care Med. 2004;169(3):386–92.
37. Choudhry S, Ung N, Avila PC, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. Am J Respir Crit Care Med. 2005;171(6):563–70.
38. Joseph CLM, Ownby DR, Peterson EL, Johnson CC. Racial differences in physiologic parameters related to asthma among middle-class children. Chest J. 2000;117(5):1336–44.
39. Celedón JC, Sredl D, Weiss ST, Pisarski M, Wakefield D, Cloutier M. Ethnicity and skin test reactivity to aeroallergens among asthmatic children in Connecticut. Chest J. 2004;125(1):85–92.
40. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007;448(7152):470–3.
41. Vercelli D. Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol. 2008;8(3):169–82.
42. Ober C, Vercelli D. Gene-environment interactions in human disease: nuisance or opportunity? Trends Genet. 2011;27(3):107–15.
43. Martinez FD, Vercelli D. Asthma. Lancet. 2013;382(9901):1360–72.
44. Kramer A, Bekeschus S, Broker BM, Schleibinger H, Razavi B, Assadian O. Maintaining health by balancing microbial exposure and prevention of infection: the hygiene hypothesis versus the hypothesis of early immune challenge. J Hosp Infect. 2013;83 Suppl 1:S29–34.
45. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: an update. Curr Opin Allergy Clin Immunol. 2013;13(1):70–7.
46. Mansour ME, Lanphear BP, DeWitt TG. Barriers to asthma care in urban children: parent perspectives. Pediatrics. 2000;106(3):512–9.
47. Laster N, Holsey CN, Shendell DG, McCarty FA, Celano M. Barriers to asthma management among urban families: caregiver and child perspectives. J Asthma. 2009;46(7):731–9.
48. Warman K, Silver EJ, Wood PR. Asthma risk factor assessment: what are the needs of inner-city families? Ann Allergy Asthma Immunol. 2006;97(1 Suppl 1):S11–5.
49. Federico MJ, Liu AH. Overcoming childhood asthma disparities of the inner-city poor. Pediatr Clin North Am. 2003;50(3):655–75; vii.
50. Warman KL, Silver EJ, Stein RE. Asthma symptoms, morbidity, and antiinflammatory use in inner-city children. Pediatrics. 2001;108(2):277–82.
51. Williams MV, Davis T, Parker RM, Weiss BD. The role of health literacy in patient-physician communication. Fam Med. 2002;34(5):383–9.
52. Birru M, Steinman RA. Online health information and low-literacy African Americans. J Med Internet Res. 2004;6(3), e26.

53. Shore SA. Obesity and asthma: possible mechanisms. J Allergy Clin Immunol. 2008; 121(5):1087–93.
54. Jen KL, Brogan K, Washington OG, Flack JM, Artinian NT. Poor nutrient intake and high obese rate in an urban African American population with hypertension. J Am Coll Nutr. 2007;26(1):57–65.
55. Smith LA, Hatcher-Ross JL, Wertheimer R, Kahn RS. Rethinking race/ethnicity, income, and childhood asthma: racial/ethnic disparities concentrated among the very poor. Public Health Rep. 2005;120(2):109–16.
56. Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. Am J Public Health. 1992;82(6):816–20.
57. Nuru-Jeter AM, Sarsour K, Jutte DP, Boyce WT. Socioeconomic predictors of health and development in middle childhood: variations by socioeconomic status measure and race. Issues Compr Pediatr Nurs. 2010;33(2):59–81.
58. Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. Immunol Allergy Clin North Am. 2011;31(1):19–39.
59. Diette GB, Hansel NN, Buckley TJ, et al. Home indoor pollutant exposures among inner-city children with and without asthma. Environ Health Perspect. 2007;115(11):1665–9.
60. Leaderer BP, Belanger K, Triche E, et al. Dust mite, cockroach, cat, and dog allergen concentrations in homes of asthmatic children in the northeastern United States: impact of socioeconomic factors and population density. Environ Health Perspect. 2002;110(4):419–25.
61. Sarpong SB, Hamilton RG, Eggleston PA, Adkinson Jr NF. Socioeconomic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. J Allergy Clin Immunol. 1996;97(6):1393–401.
62. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med. 1997;336(19):1356–63.
63. Gergen PJ, Mortimer KM, Eggleston PA, et al. Results of the National Cooperative Inner-City Asthma Study (NCICAS) environmental intervention to reduce cockroach allergen exposure in inner-city homes. J Allergy Clin Immunol. 1999;103(3 Pt 1):501–6.
64. Pandya RJ, Solomon G, Kinner A, Balmes JR. Diesel exhaust and asthma: hypotheses and molecular mechanisms of action. Environ Health Perspect. 2002;110 Suppl 1:103–12.
65. O'Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol. 2008;121(5):1133–1139. e1131.
66. Mortimer KM, Neas LM, Dockery DW, Redline S, Tager IB. The effect of air pollution on inner-city children with asthma. Eur Respir J. 2002;19(4):699–705.
67. Matsui EC. Environmental exposures and asthma morbidity in children living in urban neighborhoods. Allergy. 2014;69(5):553–8.
68. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. Clin Exp Allergy. 2005;35(5):612–8.
69. Claudio L, Stingone JA, Godbold J. Prevalence of childhood asthma in urban communities: the impact of ethnicity and income. Ann Epidemiol. 2006;16(5):332–40.
70. Saha C, Riner ME, Liu G. Individual and neighborhood-level factors in predicting asthma. Arch Pediatr Adolesc Med. 2005;159(8):759–63.
71. Wright RJ. Stress and atopic disorders. J Allergy Clin Immunol. 2005;116(6):1301–6.
72. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun. 2007;21(8):993–9.
73. Sandberg S, Paton JY, Ahola S, et al. The role of acute and chronic stress in asthma attacks in children. Lancet. 2000;356(9234):982–7.
74. Chen E, Miller GE, Walker HA, Arevalo JM, Sung CY, Cole SW. Genome-wide transcriptional profiling linked to social class in asthma. Thorax. 2009;64(1):38–43.

75. Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing and asthma. J Allergy Clin Immunol. 1998;102(6):915–20.
76. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet. 1999;354(9178):541–5.
77. Kusel MMH, de Klerk NH, Kebadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol. 2007;119(5):1105–10.
78. Henderson J, Hilliard TN, Sherriff A, et al. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. Pediatr Allergy Immunol. 2005;16(5):386–92.
79. Peck AJ, Holman RC, Curns AT, et al. Lower respiratory tract infections among American Indian and Alaska native children and the general population of U.S. children. Pediatr Infect Dis J. 2005;24(4):342–51.
80. Lowther SA, Shay DK, Holman RC, Clarke MJ, Kaufman SF, Anderson LJ. Bronchiolitis-associated hospitalizations among American Indian and Alaska native children. Pediatr Infect Dis J. 2000;19(1):11–7.
81. Sawicki GS, Smith L, Bokhour B, et al. Periodic use of inhaled steroids in children with mild persistent asthma: what are pediatricians recommending? Clin Pediatr. 2008;47(5):446–51.
82. Blixen CE, Havstad S, Tilley BC, Zoratti E. A comparison of asthma-related healthcare use between African-Americans and Caucasians belonging to a health maintenance organization (HMO). J Asthma. 1999;36(2):195–204.
83. Okelo S, Wu A, Merriman B, Krishnan J, Diette G. Are physician estimates of asthma severity less accurate in Black than in White patients? J Gen Intern Med. 2007;22(7):976–81.

Chapter 10
Health Disparities in Chronic Obstructive Pulmonary Disease

Miriam Siegel, Jerry A. Krishnan, Jamie Lamson-Sullivan, Scott Cerreta, and David M. Mannino

Key Points

- Clinicians are more likely to diagnose women who have COPD as having asthma.
- Women may be more susceptible to developing COPD.
- In the US, more women report diagnosed COPD than do men, but more men have spirometric evidence of COPD.
- COPD is more likely to develop in poorer populations.
- Research funding for COPD is much less than funding for other chronic diseases relative to the number of annual deaths.
- COPD is perceived differently from other chronic diseases as one where the patients "brought this disease on themselves."

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, mortality, and disability worldwide [1]. COPD is the fourth leading cause of death in the world and, as of 2010, the third leading cause of death in the U.S. The leading

M. Siegel • D.M. Mannino, M.D. (✉)
Department of Preventive Medicine and Environmental Health,
University of Kentucky College of Public Health, 111 Washington Avenue,
Lexington, KY 40536, USA
e-mail: dmannino@uky.edu

J.A. Krishnan
Breathe Chicago Center, Division of Pulmonary, Critical Care, Sleep & Allergy,
University of Illinois in Chicago, Chicago, IL, USA

J. Lamson-Sullivan • S. Cerreta
The COPD Foundation, Washington, DC, USA

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_10

cause of COPD in the developed world is tobacco smoking, although an increasing proportion of COPD is being seen among never smokers [2]. While tobacco smoking remains an important risk factor in the developing world, other factors, such as exposure to biomass smoke and early life respiratory infections, are also important.

Disparities are central to understanding the epidemiology and outcomes of COPD. These run the gamut from disparities in who develops disease to disparities in outcomes to disparities in how COPD is perceived and how COPD-related research is funded. This review will examine a number of key disparities in COPD, along with a vision of how these disparities could be addressed in the future.

Disparities in Diagnosis

U.S. and international guidelines define COPD as a chronic respiratory condition with persistent airflow obstruction that is usually progressive and associated with an inflammatory response in the airways and lung parenchyma due to noxious particle or gases. Evidence of airflow obstruction following use of bronchodilators is required to diagnose persistent airflow obstruction. How COPD is defined and diagnosed is a core disparity important to understanding how COPD affects populations. There are several different components to disparities in COPD diagnosis: how COPD is defined in different areas, how COPD is diagnosed in different settings, and the likelihood of receiving a COPD diagnosis in different populations.

The precise definition of COPD can vary based on local practices and physician preference. In many settings, particularly in primary care, spirometry may not be part of the routine diagnostic paradigm for COPD [3, 4]. Even when spirometry is done, interpretation may not be uniform. For example, clinicians and pulmonary function laboratories can choose from a number of different prediction equations to be used to classify patients as normal or abnormal [5]. These prediction equations can be derived locally or from national or international consortia. A potential problem is that different prediction equations have the potential to classify the same patient as abnormal or abnormal, particularly when the degree of impairment is mild. Even when using the same prediction equation, a single spirometry can be classified differently based on which specific definition is used. For example, using a lower limit of normal approach (postbronchodilator FEV_1/FVC less than lower limit of normal) to classify obstruction will classify fewer older patients as abnormal than the fixed ratio (e.g., postbronchodilator FEV_1/FVC <70 %) approach [6].

Another component of diagnostic disparities is how COPD is actually diagnosed. In many settings, COPD is being diagnosed based on history and symptoms, in the absence of any objective data. A study by Celli et al. [7] showed that in a population of veterans with a COPD diagnosis, only 31 % of patients had evidence of spirometry. This is in contrast to congestive heart failure, where in that same study 78 % of patients had an echocardiogram. The converse of this problem is the finding in multiple studies that among people with spirometric evidence of COPD, only 27 % have been given a clinical diagnosis of COPD [8].

A final component of diagnostic disparities relates to how clinicians may differ in how they diagnose COPD based on other patient factors. A classic example of this disparity is a study by Chapman et al. that presented patient histories to clinicians and varied the sex of the case presented [9]. They found that clinicians were more likely to diagnose men with COPD and women with asthma. This study was replicated by Miravitlles in Spain and showed that this diagnostic bias persisted but was less than what was previously seen [10].

Disparities in Prevalence

The most recent U.S. prevalence rates of COPD are discussed in the CDC's COPD Surveillance-United States, 1999–2011, which presents prevalence data from two surveys [11]. The first is the 2011 Behavioral Risk Factor Surveillance System (BRFSS). This telephone-based survey collected data using patient report of physician-diagnosed COPD with the question: "Have you ever been told by a doctor or other health professional that you have COPD, emphysema, or bronchitis?" Data from 475,616 respondents at least 25 years of age across all U.S. states and the District of Columbia were presented. The age-adjusted prevalence of COPD based on this measure was 6.5 % or 13,724,000 people [11].

The second data source for patient-reported physician-diagnosed COPD is the National Health Interview Survey (NHIS). The following questions were used: "Have you ever been told by a doctor or other health professional that you had emphysema?" and "During the past 12 months, have you been told by a doctor or other health professional that you had chronic bronchitis?" There were 33,014 respondents and the total 2011 national age-adjusted prevalence of COPD based on this measure was 5.7 % [11]. Note that the NHIS did not ask specifically about "COPD," which may explain the lower estimate (5.7 % vs. 6.5 %).

A problem with patient-reported COPD, which typically depends on a health care provider diagnosis, is that it is highly variable and may not be reliable [12]. This led to the development of more standardized means of assessing COPD, as shown by the Burden of Lung Disease (BOLD) study, which used spirometry to provide an estimate for the COPD burden in the population [13]. Estimates of prevalence based on patient-reported prevalence may differ when compared to estimates based on spirometry. For example, the US estimate of obstructive lung disease from the National Health and Nutrition Examination Survey (NHANES) 2007–2010 was 13.5 % for all levels of obstruction and 6.5 % for moderate to severe obstruction [14].

Differences in the prevalence of one or more risk factors for COPD in the study population also contribute to differences in the observed prevalence of COPD prevalence across studies. While cigarette smoking is a key risk factor for COPD [15], genetic, physiological, social, and environmental factors also contribute to COPD. This multiple risk factor model may help to explain some of the differences in prevalence between men and women, socioeconomic groups, and race/ethnic groups.

Gender Differences

Gender differences in COPD have been the focus of a recent review [16]. In the international BOLD study, COPD prevalence (based on spirometry) was higher in men in most countries [13]. This contrasts with the prevalence of patient-reported physician-diagnosed COPD, which in the US has been consistently 20–40 % higher among women. The 2011 BRFSS data reported by the CDC [11] showed a higher prevalence rate of COPD in women at 7.3 % compared to men at 5.7 %. There was an estimated 2,516,000 more women with COPD than men. Similarly, over the period 1999–2011, women consistently reported more physician-diagnosed COPD than men (Fig. 10.1) [11]. In contrast to patient-reported physician-diagnosed COPD, estimates of COPD using objective spirometric data from the NHANES 2007–2010 have found a higher prevalence of COPD in men (16.8 % vs. 10.4 % in women) [14]. The reasons for this discrepancy is not clear but could be related to gender differences in how men and women access the health care system (and therefore have the opportunity to be diagnosed with COPD).

There may be gender differences in the development of early onset COPD. In the COPDGene study, 66 % of subjects with severe early onset COPD were female, whereas only 43 % of older subjects with severe COPD were female [17]. Furthermore, females with COPD were 3.1 times more likely than males with COPD to have a severe early onset diagnosis.

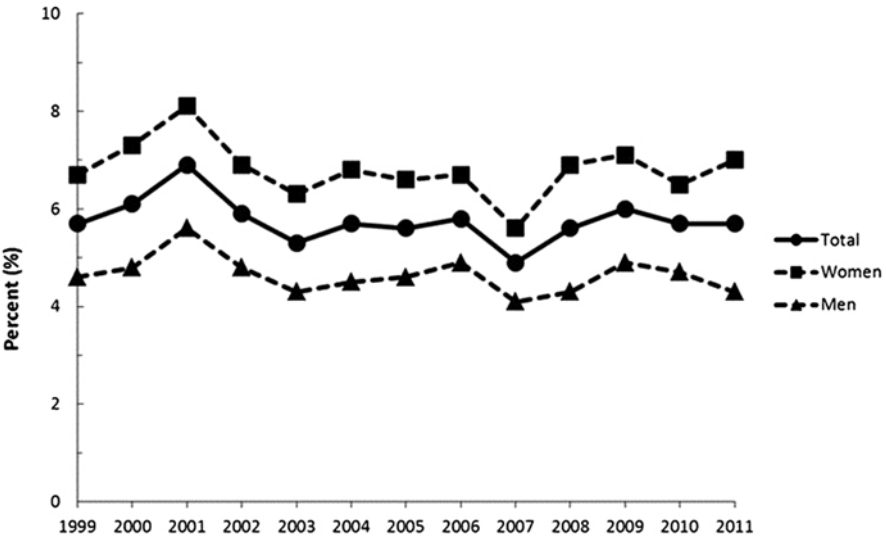

Fig. 10.1 Age-adjusted prevalence (%) of self-reported physician-diagnosed COPD among adults ≥25 years, by sex and year—United States, National Health Interview Survey, 1999–2011 [11]

Racial/Ethnic Differences

Data from the US have shown dramatic differences in COPD prevalence in different racial and ethnic groups, ranging from a low of 2.5 % in Asian/Pacific Islanders to 11.0 % in American Indian/Alaskan Natives [11] (Fig. 10.2). This can be contrasted with spirometrically determined COPD from NHANES 2007–2010 data, where 15.3 % of whites, 10.7 % of blacks, 6.3 % of Mexican-Americans, and 9.7 % of people of other races had evidence of COPD [14].

Recent data suggests that the characteristics of COPD may vary by race. For example, an analysis of the COPDGene computed tomography data suggests that blacks had less emphysema than whites (13.1 % vs. 16.1 %) [18].

As noted above, Hispanic ethnicity is protective against the development of COPD in most US populations. A study of New Mexico Hispanics that used both self-reported and DNA confirmed ethnicity found a lower risk of COPD (vs. whites: OR 0.5) and a lower risk of lung function decline (OR 0.5).

Internationally, it was demonstrated by combining both the BOLD [13] and PLATINO [19] data that countries with the lowest prevalence of COPD were predominantly Hispanic (Fig. 10.3) [20]. The large differences noted here probably reflect a combination of racial, ethnic, geographic, genetic, and exposure factors.

Socioeconomic Differences

One of the most consistent disparities in estimates of COPD prevalence is that related to socioeconomic status (SES). In a number of different studies based in different countries and using different measures of SES, a higher prevalence of

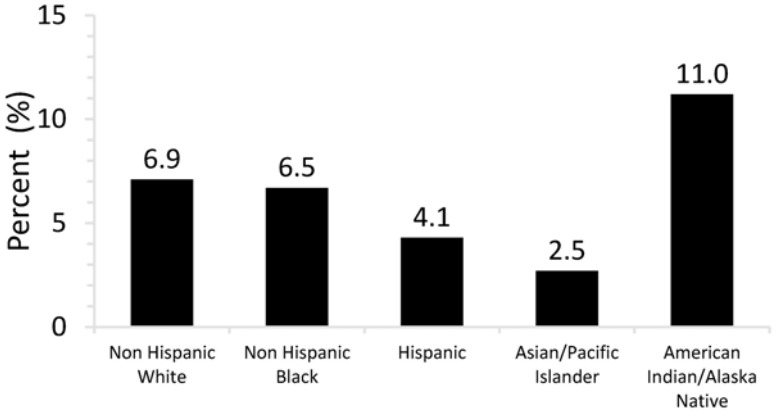

Fig. 10.2 Age-adjusted prevalence of self-reported, physician-diagnosed COPD among adults aged >25, by race/ethnicity: United States (Behavioral Risk Factor Surveillance Survey):2011 [N=475,616] data from [11]

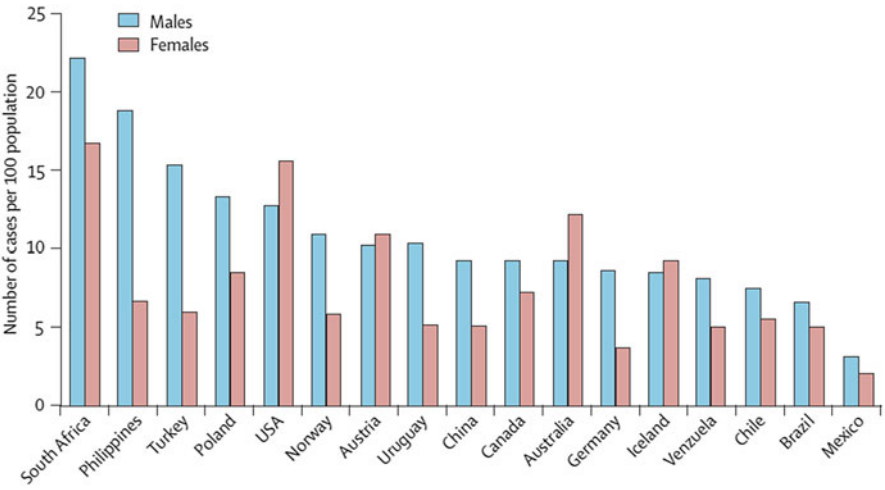

Fig. 10.3 Estimated prevalence of GOLD Stage 2 or higher COPD. Data taken from the BOLD [13] and PLATINO [19] studies. Estimates are for small regions and do not necessarily represent national prevalence estimates [20]

COPD is observed in lower SES populations (Table 10.1). Although a lower SES is typically related to COPD risk factors such as smoking, multivariate regression models continue to show an SES gradient. For example, in the Yin study of a Chinese population, the low-income group had a significantly higher risk of COPD (OR 2.1) relative to the high-income group.

Geographic Differences

As noted above, the BOLD and PLATINO studies demonstrated a great deal of variability in the prevalence of COPD between different populations in different countries (Fig. 10.3) [13]. In the BOLD study, COPD among women ranged from 5·1 % in Guangzhou, China, to 16·7 % in Cape Town, South Africa, and in men it ranged from 8·5 % in Reykjavik, Iceland, to 22·2 % in Cape Town, South Africa.

In the United States, the rate of COPD varies from state to state, from a low of 4.3 % in Utah to a high of 10.6 % in Kentucky [11]. Smaller area data are not yet available for COPD prevalence, although it is highly likely that prevalence rates in counties or health districts also show considerable variation. This variation is related to a number of factors including the key COPD risk factors like smoking and occupational exposures, in addition to poverty, early life respiratory infections, diet, physician diagnostic differences, and other factors [20].

Table 10.1 Socioeconomic status and COPD prevalence from selected studies

Author/year	Country	SES indicator	Level	COPD prevalence men or overall (%)	COPD prevalence women (%)
Chen/2000 [40]	Canada	Income adequacy	High	1.6	2.6
			Middle	2.4	4.6
			Low	6.6	6.6
Ferre/2012 [41][a]	France	Annual income	High	1.9	
			Middle	3.6	
			Low	3.4	
			Very Low	5.3	
Kanervisto/ 2011 [42]	Finland	Household income	High	3.1	
			Middle	3.4	
			Low	9.2	
Yin/2011 [43]	China	Income	High	2.0	
			Middle	2.4	
			Low	4.2	
Ford/2013 [14]	United States	Education (years)	>12	12.4	
			12	15.7	
			<12	14.3	
Danielsson/ 2012 [44]	Sweden	Education (years)	>12	11.4	
			12	12.6	
			<12	28.0	

[a]Chronic bronchitis

Disparities in Treatment

Access to care and use of efficacious medications can help avoid harm in patients with COPD. Few studies have specifically examined differences in access to care or use of COPD treatments across patient populations, but the available evidence suggests that disparities in treatment exist across different patient groups. Tiotropium, introduced in the U.S. in 2004, is a long-acting analog of the inhaled anticholinergic medication ipratropium bromide. In placebo-controlled randomized clinical trials, tiotropium has been shown to significantly improve health-related quality of life (St. George's Respiratory Questionnaire) and dyspnea (Transitional Dyspnoea Index); lung function; and lower the risk of exacerbations, hospitalizations, and mortality [21–23]. In a study conducted 2 years after the introduction of tiotropium in the U.S., investigators observed that a lower SES was strongly associated with decreased odds of using tiotropium, even after taking into account measures of disease severity [24]. Patients with lower levels of education (less than or equal to high school) or income (<$20,000) had one-third the odds of using tiotropium compared to their more advantaged counterparts. Results of a more recent

study among patients enrolled in COPDGene (published as an abstract in 2010) also suggest that black race is associated with significantly lower use of tiotropium [25]. Differences in access to therapy probably exist for other types of COPD interventions, including medications, noninvasive ventilation, and lung transplantation [26, 27]. Thus, these findings raise concerns about the potential for differences in the quality of care contributing to COPD disparities in outcomes.

Disparities in Outcomes

This section will examine differences and disparities in morbidity and mortality among patients with COPD.

Morbidity

Key measures of COPD-related morbidity include exacerbation events and health-related quality of life (HRQOL). Exacerbations of COPD are related to a number of factors [28] and commonly result in emergency room visits and hospitalizations. In 2010 the United States had an estimated 699,000 hospitalizations, or an age-adjusted rate of 32.2 per 10,000 U.S. civilians, for patients at least 25 years of age with a first-listed diagnosis of COPD [11]. Hospitalization rates were similar between men (31.6 per 10,000) and women (33.4 per 10,000) but were higher in blacks (39.5 per 10,000) compared with whites (29.5 per 10,000). This is in spite of a national trend observed with hospitalization rates decreasing for all adults between 1999 and 2010 [11].

When observing only Medicare enrollees of at least 65 years of age, there were 312,654 hospital discharge claims, or an age-adjusted rate of 11.18 per 1000 enrollees, with a first-listed diagnosis of COPD in 2010. Hospitalization rates for Medicare enrollees were similar for men (11.6 per 1000) and women (10.0 per 1000). With respect to race and ethnicity, the hospitalization rates were the highest for Native American enrollees (13.2 per 1000), followed by black enrollees (12.4 per 1000), white enrollees (11.3 per 1000), Hispanic enrollees (9.7 per 1000), and Asian enrollees (4.8 per 1000). From 1999 to 2010, Medicare hospitalizations decreased for enrollees overall and for men, but not significantly for women or any specific race/ethnicity group (Fig. 10.4) [11].

A COPD-related hospitalization increases the risk of subsequent mortality independent of the baseline level of lung function [29]. African Americans hospitalized with COPD exacerbations have a higher 30-day readmission rate compared with white patients (23.1 % vs. 20.5 %) [30]. Income is also associated with 30-day readmission rates after COPD exacerbations; patients living in areas with a median household income in the lowest quartile have a higher readmission rate compared with patients living in areas with the highest quartile of income (21.5 % vs. 20.2 %).

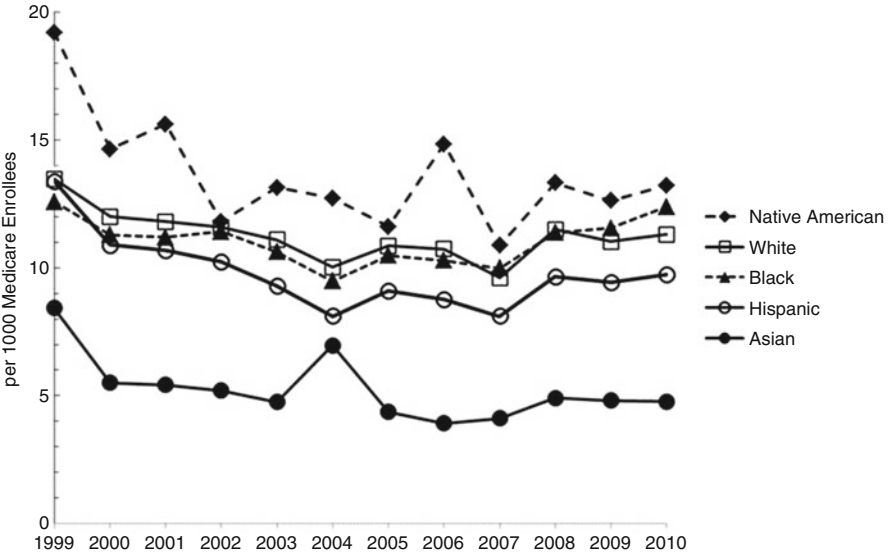

Fig. 10.4 Race-specific age-adjusted rates (per 1000 Medicare enrollees) of Medicare hospitalizations for COPD as the first-listed discharge diagnosis among Medicare enrollees aged >65 years, by year—United States, Medicare Part A hospital claims, 1999–2010 [11]

Many factors can affect HRQOL in COPD patients, including age and sex. Other factors that affect HRQOL, such as lung function, smoking history, current smoking status, and education, tend to vary by race. However, even after adjusting for these and additional confounders, disparities in HRQOL can still be found between African Americans and Caucasians. Data from the COPDGene study was used to examine differences in HRQOL according to the St. George Respiratory Questionnaire (SGRQ) [31]. For COPD patients with no exacerbations reported in the prior year, SGRQ scores were similar for African Americans and Caucasian patients. However, African American patients that reported exacerbations in the previous year averaged 1.89 points higher (i.e., worse HRQOL) on the SGRQ per exacerbation than Caucasians. Additionally, more African Americans had at least one exacerbation requiring hospitalization (32 %) than Caucasians (16 %). Of those patients reporting exacerbations requiring hospitalization, African Americans tended to score 4.19 points higher on the SGRQ measure per exacerbation than Caucasians.

Similarly, outcomes of COPD severity, pulmonary function, physical function limitations, and risk of exacerbation have been shown to vary by certain demographic factors. A cohort of COPD patients from the Function, Living, Outcomes, and Work study were analyzed for associations between outcomes and demographic factors of race, education, and income after controlling for a multitude of covariates [32]. Both lower education and lower household income were associated with higher COPD severity and poorer lung function (FEV1%) when compared to their

high education and income counterparts. Lower income groups also performed poorer in physical function than did the high-income group. The lowest education and income groups were found to have more severe airflow obstruction (FEV1/FVC) and a higher risk of exacerbation requiring hospitalization when compared to the highest education and income groups. The lowest education group also showed poorer physical function relative to the highest education group. With respect to race, black subjects had better lung function (FEV1%) but poorer physical function when compared to white subjects.

Mortality

There were 133,575 deaths in the U.S. in 2010 that were attributed to COPD, corresponding to an age-adjusted rate of 63.1 per 100,000 people. This death rate decreased from 1999 to 2010 for men, but did not change in women or overall. Death rates were highest in 2010 among whites (70.2 per 100,000), followed by American Indian/Alaska Natives (62.9 per 100,000), blacks (41.8 per 100,000), Hispanics (28.5 per 100,000), and Asian/Pacific Islanders (19.0 per 100,000) [11] (Fig. 10.5). Of note, between 1980 and 2002, death rates for African American COPD patients increased at a higher rate than for Caucasian COPD patients [33].

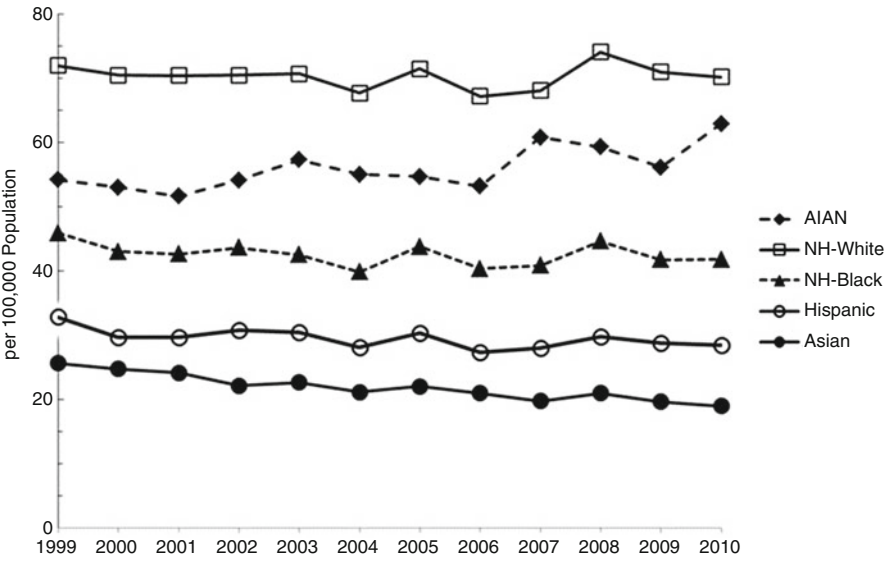

Fig. 10.5 Race-specific age-adjusted death rates (per 100,000) for COPD as the underlying cause of death among adults aged >25 years, by year—United States, Mortality Component of the National Vital Statistics System, 1999–2010 [11]

Disparities in Research Funding

Another key disparity in COPD relates to the research funding this disease receives relative to the impact of the disease on the US population. When Gillum et al. evaluated this looking at 2006 data, they found that COPD was one of the most underfund diseases by the National Institutes of Health relative to the number of disability adjusted life years for COPD [34] (Fig. 10.6). Since 2006, COPD federal funding has increased dramatically with projects such as COPDGene [35] and the Long-Term Oxygen Treatment Trial (LOTT).

Disparities in Patient and Public Perception of COPD

Another key historical disparity is how COPD has been perceived by patients and the public. This is, in large part, due to COPD's association with cigarette smoking in most of the developed world [36]. People tend to "blame" themselves for having

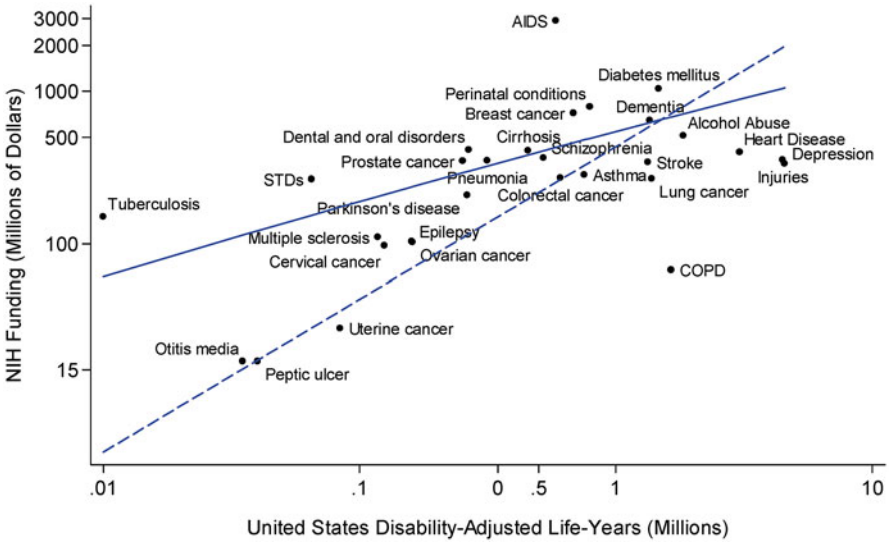

Fig. 10.6 NIH Funding in 2006 and US Disease Burden in DALYs in 2004 for 29 Common Medical Conditions. The *solid line* represents the results of a traditional multivariable analysis, showing the relationship between US disease-specific DALYs burden and actual 2006 NIH funding dollars. The *dashed line* projects NIH funding levels in a similar multivariable model that requires that a disease with no burden receives no funding (constrained model). Though the models produce similar results, several diseases that would be considered overfunded in one model are considered underfunded in the other. For example, cervical cancer appears to be overfunded relative to the *dashed line*, while it is underfunded relative to the *solid one* [34]

"brought this disease upon themselves" and are embarrassed to even admit that they have the disease. Even among patients who have stopped smoking many years before there is a tendency for self-blame by saying "I should have stopped smoking earlier." Many of these same features are often associated with the tobacco-related disease of lung cancer, where a typical question asked of a newly diagnosed patient revolves around their smoking history, again with the presumption that this person brought this disease upon himself.

Cigarette smoking is linked to a number of other diseases, including heart disease, colon cancer, cervical cancer, and diabetes [37], yet none of these diseases suffer from the "shame and blame" attitudes that permeate COPD.

Fortunately, these attitudes are changing. In the US over 25 % of adults with evidence of COPD have never smoked [11]. In addition, in recent years patients with COPD have become more empowered about their disease management in general and their expectations of better therapies and better outcomes compared to what was expected 20 years ago. In 2011 the CDC released a task force report to approach COPD as a public health problem, going well beyond the "burning cigarette" as the only area where interventions could occur [38].

Resources to Learn More About COPD

Prior to the formation of the U.S. COPD Coalition in 2001 and the COPD Foundation in 2004, there were no patient advocacy organizations solely dedicated to serving the COPD community and as a result, resources for patients were scarce. Today there are numerous COPD-related resources available online that provide high-quality information for health care providers and patients and their families but disparities in the dissemination and use of these materials still exist. Some of these are noted below.

For Health Care Providers

1. COPD Foundation—www.copdfoundation.org 1-866-316-(COPD) 2673
   The COPD Foundation, with guidance from its Medical and Scientific Advisory Committee produced the Pocket Consultant Guide for the Diagnosis and Management of COPD and a corresponding interactive website for healthcare providers to discuss clinical issues in COPD. The COPD Foundation also publishes a quarterly clinical magazine on lung health, the *Lung Health Professional* and produces several live and enduring CME resources throughout the year.
2. Global Initiative on Chronic Obstructive Lung Disease (GOLD)—www.goldcopd.org

GOLD resources available for download include the Global Strategy for Diagnosis, Management, and Prevention of COPD and its corresponding At-A-Glance Desk Reference and Pocket Guide.

3. American Lung Association—www.lung.org

   The ALA has developed the COPD Action Plan document that providers can give to patients to help them understand what medication they are taking, signs of exacerbations, and what to do based on certain physical symptoms.

4. American Thoracic Society—www.thoracic.org

   Standards for the Diagnosis and Management of COPD are available for download on the ATS website along with several web-based pages highlighting key points for the management of specific issues in COPD, monthly clinical case web features on multiple lung health issues including COPD and references related to coding and billing. ATS publishes the American Journal of Respiratory and Clinical Care Medicine and Annals of the ATS, both of which address COPD research.

5. European Respiratory Society—www.ersnet.org

   ERS publishes the European Respiratory Journal and a number of topical handbooks and position statements related to COPD, coauthors COPD Guidelines with the ATS and puts on a large respiratory congress each year where original COPD research is presented.

6. National Heart, Lung and Blood Institute—www.nhlbi.nih.gov

   NHLBI, through their COPD: *Learn More Breathe Better* Campaign provides COPD essentials fact sheets for providers along with periodic workshops and research funding in COPD.

For Patients and Their Families

1. COPD Foundation—www.copdfoundation.org 1-866-316-(COPD) 2673

   The COPD Foundation has created an extensive list of resources specifically for COPD patients and their families. The Information Line is staffed by trained patients and caregivers and available toll-free Monday–Friday 9 am–9 pm ET. The *COPD Digest* is a free quarterly publication with clinical, lifestyle, and policy information related to COPD. Comprehensive educational materials are available free for download or can be ordered by patients for free by calling the COPD Information Line.

2. Alpha-1 Foundation—www.alpha-1foundation.org

   Individuals with Alpha-1 Antitrypsin Deficiency can access educational materials written specifically about the genetic condition. The Alpha-1 Foundation also provides a free confidential, mail-based, testing program for Alpha-1.

3. American Lung Association—www.lung.org

The ALA supports the Better Breathers Clubs, a network of support groups for individuals with all types of lung disease. In addition, the ALA hosts a lung helpline and produces written educational materials about COPD.

4. WebMD—www.webmd.com

   WebMD hosts the COPD Help Center, a virtual home for information about COPD symptoms, diagnosis, treatment, and more.

5. American Association for Respiratory Care—www.yourlunghealth.org

The American Association for Respiratory Care is a professional association of respiratory therapists and other allied health practitioners who assist physicians in the treatment and care of patients with lung disorders. Education of patients is an important part of their mission. This web site provides useful information on a number of respiratory diseases and their treatments.

Looking Toward the Future

A great deal of progress has been made in reducing COPD-related disparities in the past 20 years. Moving away from the sole focus on tobacco smoking has been key. This shift is critical, because even if every smoker in the country were to stop smoking today, the morbidity and mortality related to COPD would remain unchanged for the next 25–30 years [39]. Increasing research funding to better understand who is at risk and how interventions can be better targeted is also important.

Conclusion

COPD represents a group of related diseases that have been associated with a number of disparities over the years. These range from disparities in diagnosis, treatment, and outcomes to disparities in public perception and research funding. In recent years, there has been movement toward the elimination of these disparities by increasing research funding, developing better therapies, and increasing awareness of the risk factors beyond tobacco smoke that lead to COPD. The future for COPD looks very different from its past, with movement from nihilism to optimism, and a greater global acceptance of the diversity of disease phenotypes, therapies, and outcomes.

Acknowledgments We gratefully acknowledge funding by the Patient-Centered Outcomes Research Institute (CE-1304-6490 and IH-12-11-4365; Krishnan)

Conflict of Interest Statement: DMM has served as a consultant for Boehringer Ingelheim, GlaxoSmithKline, Astra-Zeneca, Novartis, Merck and Forest and has received research grants from GlaxoSmithKline, Novartis, Boehringer-Ingelheim, Forest and Pfizer. MS, JK. JLS, and SC report no conflicts of interest.

References

1. CDC. Chronic obstructive pulmonary disease among adults—United States, 2011. MMWR Morb Mortal Wkly Rep. 2012;61(46):938–43.
2. Ford ES, Mannino DM, Zhao G, Li C, Croft JB. Changes in mortality among US adults with COPD in two national cohorts recruited from 1971-1975 and 1988-1994. Chest. 2012;141(1):101–10.
3. Monteagudo M, Rodriguez-Blanco T, Parcet J, Penalver N, Rubio C, Ferrer M, et al. Variability in the performing of spirometry and its consequences in the treatment of COPD in primary care. Arch Bronconeumol. 2011;47(5):226–33.
4. Joo MJ, Au DH, Fitzgibbon ML, McKell J, Lee TA. Determinants of spirometry use and accuracy of COPD diagnosis in primary care. J Gen Intern Med. 2011;26(11):1272–7.
5. Roche N, Dalmay F, Perez T, Kuntz C, Vergnenegre A, Neukirch F, et al. FEV1/FVC and FEV1 for the assessment of chronic airflow obstruction in prevalence studies: do prediction equations need revision? Respir Med. 2008;102(11):1568–74.
6. Lamprecht B, Schirnhofer L, Kaiser B, Buist SA, Mannino DM, Studnicka M. Subjects with discordant airways obstruction: lost between spirometric definitions of COPD. Pulm Med. 2011;2011:780215.
7. Damarla M, Celli BR, Mullerova HX, Pinto-Plata VM. Discrepancy in the use of confirmatory tests in patients hospitalized with the diagnosis of chronic obstructive pulmonary disease or congestive heart failure. Respir Care. 2006;51(10):1120–4.
8. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64(10):863–8.
9. Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. Chest. 2001;119(6):1691–5.
10. Miravitlles M, de la Roza C, Naberan K, Lamban M, Gobartt E, Martin A, et al. Attitudes toward the diagnosis of chronic obstructive pulmonary disease in primary care. Arch Bronconeumol. 2006;42(1):3–8.
11. Ford ES, Croft JB, Mannino D, Wheaton AG, Zhang X, Giles WH. COPD surveillance-United States, 1999-2011. Chest J. 2013;144(1):284–305.
12. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28(3):523–32.
13. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741–50.
14. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988-1994 to 2007-2010. Chest. 2013;143(5):1395–406.
15. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med. 2011;11:36.
16. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med. 2007;176(12):1179–84.
17. Foreman MG, Zhang L, Murphy J, Hansel NN, Make B, Hokanson JE, et al. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. Am J Respir Crit Care Med. 2011;184(4):414–20.
18. Hansel NN, Washko GR, Foreman MG, Han MK, Hoffman EA, DeMeo DL, et al. Racial differences in CT phenotypes in COPD. COPD. 2013;10(1):20–7.

19. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366(9500):1875–81.
20. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370(9589):765–73.
21. Kaplan A. Effect of tiotropium on quality of life in COPD: a systematic review. Prim Care Respir J. 2010;19(4):315–25.
22. Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(10):948–55.
23. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543–54.
24. Blanc PD, Eisner MD, Yelin EH, Earnest G, Balmes JR, Gregorich SE, et al. Socioeconomic gradients in tiotropium use among adults with COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(3):483–90.
25. Mamary AJ, Gaughan JP, Murphy J, Vance GB, Criner GJ, COPDGene Investigators**.** Disparities in COPD diagnosis and treatment are determined by region, race, gender and education. American Journal of Respiratory and Critical Care Medicine, Vol. 181, Meeting Abstracts; 2010.
26. Wille KM, Harrington KF, deAndrade JA, Vishin S, Oster RA, Kaslow RA. Disparities in lung transplantation before and after introduction of the lung allocation score. J Heart Lung Transplant. 2013;32(7):684–92.
27. Lederer DJ, Benn EK, Barr RG, Wilt JS, Reilly G, Sonett JR, et al. Racial differences in waiting list outcomes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177(4):450–4.
28. de Oca MM, Tálamo C, Halbert RJ, Perez-Padilla R, Lopez MV, Muiño A, et al. Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities. The Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) Study. Chest J. 2009;136(1):71–8.
29. Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. Thorax. 2011;66(7):585–90.
30. Elixhauser A, Au DH, Podulka J. Readmissions for chronic obstructive pulmonary disease, 2008: statistical brief #121. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs, Rockville; 2011.
31. Han MK, Curran-Everett D, Dransfield MT, Criner GJ, Zhang L, Murphy JR, et al. Racial differences in quality of life in patients with COPD. Chest. 2011;140(5):1169–76.
32. Eisner MD, Blanc PD, Omachi TA, Yelin EH, Sidney S, Katz PP, et al. Socioeconomic status, race and COPD health outcomes. J Epidemiol Community Health. 2011;65(1):26–34.
33. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. Chest. 2002;121(5 Suppl):121S–6.
34. Gillum LA, Gouveia C, Dorsey ER, Pletcher M, Mathers CD, McCulloch CE, et al. NIH disease funding levels and burden of disease. PLoS One. 2011;6(2), e16837.
35. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010;7(1):32–43.
36. Arne M, Emtner M, Janson S, Wilde-Larsson B. COPD patients perspectives at the time of diagnosis: a qualitative study. Prim Care Respir J. 2007;16(4):215–21.
37. US Department of Health and Human Services. The health consequences of smoking-50 years of progress: a report of the Surgeon General. Atlanta: US Department of Health and Human Services; 2014.
38. Centers for Disease Control and Prevention. Public health strategic framework for COPD prevention. Washington, DC: Centers for Disease Control and Prevention; 2011.
39. Najafzadeh M, Marra CA, Lynd LD, Sadatsafavi M, FitzGerald JM, McManus B, et al. Future impact of various interventions on the burden of COPD in Canada: a dynamic population model. PLoS One. 2012;7(10), e46746.

40. Chen Y, Breithaupt K, Muhajarine N. Occurrence of chronic obstructive pulmonary disease among Canadians and sex-related risk factors. J Clin Epidemiol. 2000;53(7):755–61.
41. Ferre A, Fuhrman C, Zureik M, Chouaid C, Vergnenegre A, Huchon G, et al. Chronic bronchitis in the general population: influence of age, gender and socio-economic conditions. Respir Med. 2012;106(3):467–71.
42. Kanervisto M, Vasankari T, Laitinen T, Heliovaara M, Jousilahti P, Saarelainen S. Low socioeconomic status is associated with chronic obstructive airway diseases. Respir Med. 2011;105(8):1140–6.
43. Yin P, Zhang M, Li Y, Jiang Y, Zhao W. Prevalence of COPD and its association with socioeconomic status in China: findings from China Chronic Disease Risk Factor Surveillance 2007. BMC Public Health. 2011;11:586.
44. Danielsson P, Olafsdottir IS, Benediktsdottir B, Gislason T, Janson C. The prevalence of chronic obstructive pulmonary disease in Uppsala, Sweden—the Burden of Obstructive Lung Disease (BOLD) study: cross-sectional population-based study. Clin Respir J. 2012; 6(2):120–7.

Chapter 11
Health Disparities and Tuberculosis

Eyal Oren

Key Points

- Poverty and low socioeconomic status are associated with differential access to health care and service delivery, resulting in differential TB outcomes across populations.
- Broad social determinants, such as housing conditions, social networks, and social support, are strong drivers of TB epidemics.
- The disproportionate burden of TB among racial and ethnic groups is largely due to differences in living and social conditions.
- TB rates vary highly by country and location and cluster in space.
- Interventions to address inequities and links between TB and risk factors include health sector interventions, intersectoral policies impacting across society, and measurement and research.

Preface

> Of all the forms of inequality, injustice in health care is the most shocking and inhumane—Dr. Martin Luther King, Jr., 1966.

Martin Luther King, Jr.'s comment about injustice in health care captures the conundrum of health disparities that exist worldwide. Health disparities refer to gaps in the quality of health and health care related to gender, race, ethnicity, socioeconomic status (SES), and other sociodemographic characteristics. The term disparities describes both differentials in health status, such as disease prevalence,

E. Oren, Ph.D., M.S. (✉)
Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, 1295 N. Martin Ave, Tucson, AZ 85724, USA
e-mail: eoren@email.arizona.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_11

incidence, or mortality, as well as disparities in health care, such as differences in the preventive, diagnostic, and treatment services offered to people with similar health conditions. Health disparities continue to be a major public health problem affecting health systems around the globe, persisting over both time and the life course, to the extent that most major health agencies and projects are now addressing the issues in their goal statements. For example, Healthy People 2020, the 10-year national strategic plan for improving the health of all Americans, has committed to "achieve health equity, eliminate disparities, and improve the health of all groups" as one of its four overarching goals [1]. On a related note, work over the last decade, according to Steven Woolf of Virginia Commonwealth University, has shown that "achieving equity may do more for health than perfecting the technology of care" [2]. Such health disparities are particularly relevant to tuberculosis (TB).

Worldwide, one out of three persons is infected with *Mycobacterium tuberculosis*, with 1.5 million deaths due to TB [3]. TB continues to affect many communities in the United States and elsewhere disproportionately and unequally [4]. TB is a bacterial disease spread from person to person through the air. But risk of exposure to TB, the risk for developing TB once infected, as well as treatment access and provision are not equal among different population groups. Notable differences in TB risk exist across racial and ethnic groups, socioeconomic strata, gender, immigration status, and geographic location. In the U.S., foreign-born persons have case rates 11.5 times higher than US-born persons, and among the US born, the largest disparities are between blacks and whites; where TB rates in blacks are 5.8 times greater than among whites, and distribution is geographically heterogeneous with California, Texas, New York, and Florida reporting half of all TB cases in 2012 [4].

Poor ventilation and overcrowding in homes, workplaces, and communities increase the likelihood of uninfected individuals being exposed to TB infection [5, 6]. Individuals with TB symptoms such as a persistent cough often face significant social and economic barriers that delay their contact with health systems in which an appropriate diagnosis might be made, including difficulties in transport to health facilities, fear of stigmatization if they seek a TB diagnosis, mistrust of the medical community, and lack of social support to seek care when they fall sick [7–9]. A conceptual model illustrating one proposed framework linking social and economic exposures and TB outcomes is presented in Fig. 11.1. The model illustrates both the pathways through which socioeconomic position can influence TB health outcomes, as well as interventions that can potentially ameliorate low socioeconomic position (e.g., cash transfers, microfinance services).

This chapter focuses on the evidence of health disparities in tuberculosis, with emphasis placed on the intertwined root causes of these disparities, namely, differences in TB health outcomes by economic and social opportunities and resources. The chapter focuses equally on the disparities across three main axes: SES, differences across populations, and geographic location. While each of these content areas has its own large body of supporting literature, they are all clearly linked by the overriding "root causes" mentioned earlier. These root causes, as well as current thinking regarding how to ameliorate their influence in the context of TB, will be discussed below.

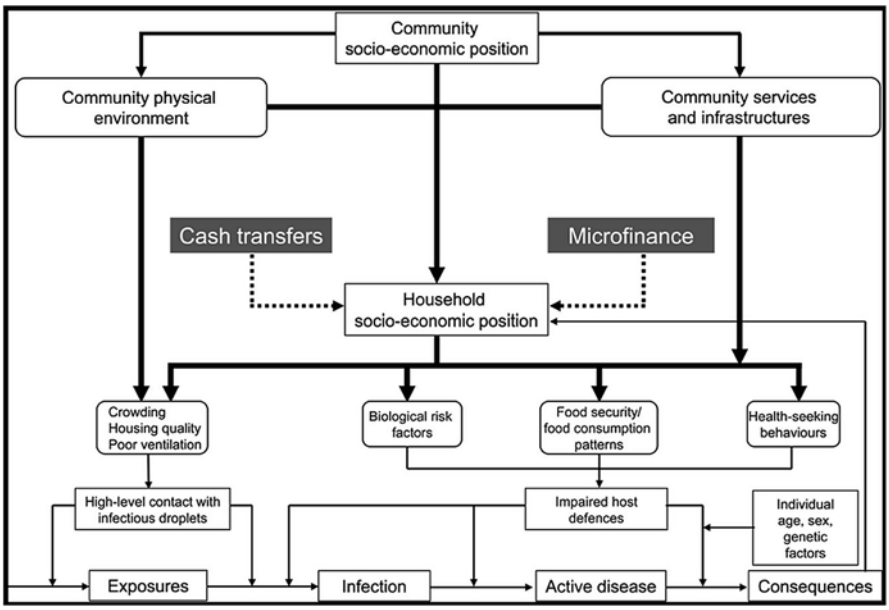

Fig. 11.1 Conceptual framework for TB Control, with posited interventions targeting socioeconomic position at household level. Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright The Union. Boccia D, Hargreaves J, Lonnroth K, et al. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications. *The international journal of tuberculosis and lung disease*. Jun 2011;15 Suppl 2:S37-49

Socioeconomic Factors and Tuberculosis Disparities

The decline in TB in the United States began before the introduction of the BCG vaccine in 1921 and chemotherapy in 1944, so was likely due more to improved social conditions and the natural history of the pandemic than medical advances in treatment and prevention [10]. McKeown has noted that the public health effects of medical treatment were overemphasized during the early to mid-twentieth century [11]. Research has demonstrated a strong relationship between SES and an increased risk of being affected by health disparities [12]. Strong stepwise gradients are observed between increasing social advantage, as measured primarily by income, education and occupational grade, and improvements in health [13, 14]. Yet, while TB has been recognized as a "social disease" since the nineteenth century, going back at least to Engels' The Condition of the Working Class in England [15], the global TB control paradigm has focused mainly on cutting transmission through early case detection and effective treatment, with biomedical interventions at the core of the global strategy [16]. Social factors describe the distribution of TB

disease, as well as allow for effective targeted testing and prevention efforts that require an understanding of the demographics of targeted populations, which include factors such as SES. More importantly, because the inequitable distribution of TB throughout the world clusters particularly among the poor and among minorities [17, 18], structural approaches to prevention that emphasize sociocultural, political, economic, and environmental factors can potentially greatly mitigate some of the inequities in the incidence, mortality, and morbidity of TB between different population groups and countries [19].

In recent years, there has been growing emphasis, both in the scientific literature and in the policy realm, on the social determinants of tuberculosis disparities. Notably, the profile of this work has been raised through recent initiatives by the World Health Organization (WHO) Commission on the Social Determinants of Health [20] and the U.S. Centers for Disease Control (CDC) [21]. The WHO Stop TB Department has recognized the need to broaden the strategy to include more preventive efforts, which include social, economic, and environmental interventions [22].

Tuberculosis and Poverty

Tuberculosis is regarded as a disease of poverty and many aspects of low SES, for example, overcrowding and malnutrition, are accepted individual- and household-level risk factors for the disease. Inequities can be explained in terms of differences in socioeconomic status and other structural factors that influence exposure to risk, vulnerability, and the ability to recover after becoming ill [23].

As with many other diseases, the TB burden follows a clear socioeconomic gradient, with the poorest at the most elevated risk [24, 25]. This most fundamental of socioeconomic measures, poverty, is ineluctably paired with individual or household income. Yet poverty is multidimensional, including material well-being but also absence of infrastructure or a lack of input [26]. In the TB literature, markers of poverty range from individual indicators of household poverty status, to aggregate indices across geographical areas such as neighborhoods, to select populations who are considered socially vulnerable.

In Vienna in the early 1900s, the wealthiest portion of the city had a death rate from tuberculosis of 11 per 10,000 of the population; the income tax payers amounted to 25 % of the population, and the illegitimate births 0.8 per 1000, whereas in the poorest section of the city, the death rate from tuberculosis was 67 per 10,000; the income tax payers 9.2 % of the population, and the illegitimate births 9.2 per 1000 [27]. Almost a century later, the incidence of TB in central Harlem in 1990 was 32 times that of neighboring and more affluent sections of Manhattan [28]. In the United States, in both New York City and Seattle, neighborhood poverty has recently been strongly associated with TB incidence [29, 30]. Ecologic studies conducted in both the United States and Britain have found crude associations between tuberculosis rates across areas and low levels of education,

high levels of poverty, less government social support, social deprivation, and income inequality [31–34]. For example, Fig. 11.2a, b shows both TB incidence rates, as well as the percentage of persons below the poverty level per zip code tabulation area (ZCTA) for an urban county in Georgia. A strong correlation is observed between the poorest ZCTAs and the highest TB incidence rates. Evidence from ecologic and multilevel studies in Brazil, South Africa, and other countries supports the existence of this relationship in middle- and low-income countries [35–41]. Finally, individual-level studies of the link between low SES and high risk of tuberculosis have found associations in poorer, high tuberculosis-burden settings [42, 43]. Similarly, the magnitude of all TB death rates has been found highest in low-household income areas, followed by middle- and high-income areas [44]. The

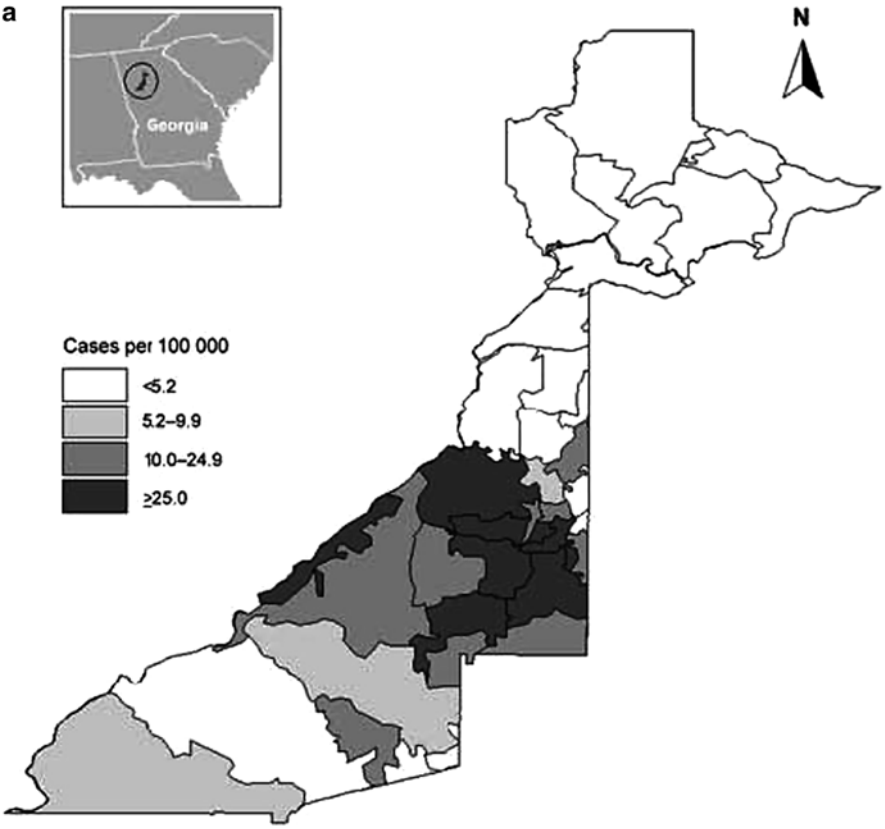

Fig. 11.2 (**a**) Average annual incidence of TB per 100 000 (based on cases from 1997 to 2001) in Fulton County, Georgia, USA, by Zip Code Tabulation Area. (**b**) Percentage of persons below the poverty level. Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright The Union. Lopez De Fede A, Stewart JE, Harris MJ, Mayfield-Smith K. Tuberculosis in socio-economically deprived neighborhoods: missed opportunities for prevention. *The international journal of tuberculosis and lung disease*. Dec 2008;12(12):1425-1430

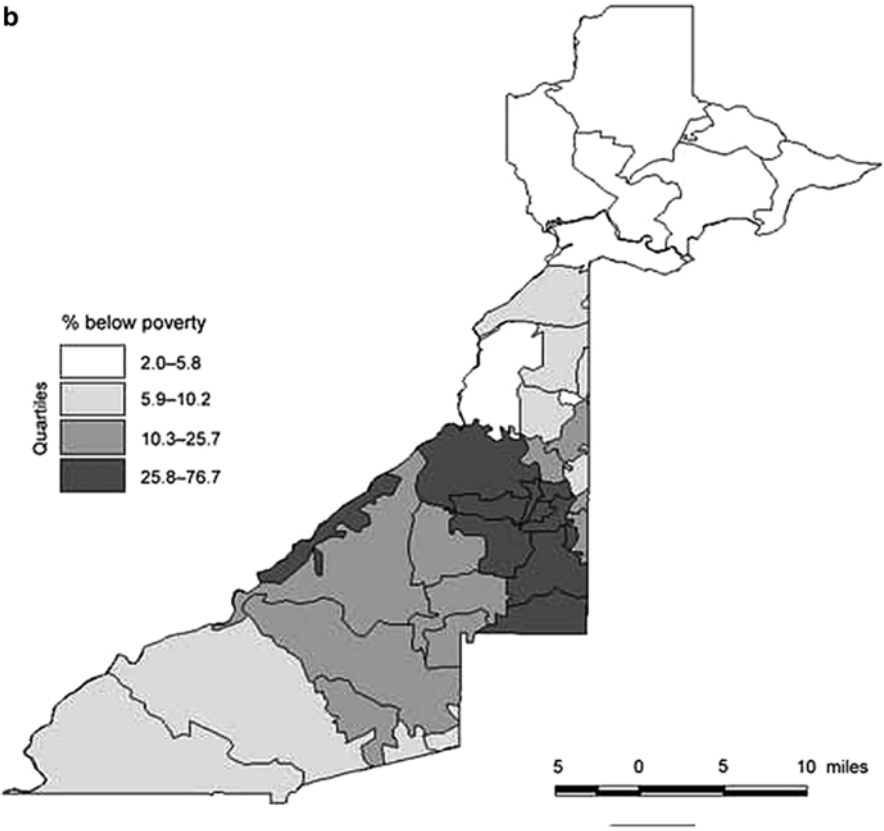

Fig. 11.2 continued

association between infection and SES is not as clear. Tuberculin skin test positivity was least frequent in households with higher educational level, income, skilled occupations, and room size [45, 46]. Other studies have found that the risk of tuberculin skin test positivity was not associated with socioeconomic indicators [47, 48] or that infection as measured through the Quantiferon blood test actually increased with SES, possibly because wealthier homes were less well ventilated [49].

Crowding (and Density)

One would expect that greater density would allow for higher contact rates with an infectious individual, and thus elevated risk of disease transmission [50]. In 1996–2000, after adjusting for sociodemographic factors, Wanyeki et al. [5] used residential addresses to geocode active TB cases reported in Montreal. They found that dwelling and building features, particularly dwellings in taller and new buildings, with lower resale value, and dwellings on blocks with high residential density

as well as crowding were associated with TB occurrence. Similarly, in New Zealand, TB incidence has shown to be associated with household crowding [51], and TB case rates were significantly higher in the highest crowding quartile of zip codes in the US [52]. Children living in areas of the Bronx in which over 12 % of homes were severely overcrowded were over fivefold more likely to develop active TB [53]. In First Nations communities in Canada, higher TB disease rates were observed in communities with more people living in a room (housing density) and an increase in risk of >2 TB cases occurring for every 0.1 increase in persons per room was observed [54]. While greater population density might equate with more shared air with a TB case, communities with overcrowded housing may also experience a higher prevalence of latent TB infection, or risk factors for progression from TB infection to disease. However, Myers et al. [55] found a protective effective for crowding (after adjustment for race, ethnicity, immigration, and socioeconomic factors) and no effect for population density in pediatric TB cases within California. They explained this as partly due to correlation with other variables that better explained the variability in tuberculosis cases, such as race/ethnicity, lower median incomes, and immigration. As well, to be discussed further below, crowding may be associated with a more tightly woven social network that could protect against disease [25].

Other Socioeconomic Factors

Unemployment, a factor expressing lower social class, is associated with disparate TB rates as well. Among the Inuit, it has been described as one of the major determinants of risk with those on social funds or unemployed over four times more likely to have a TB infection than workers or students [56]. The greatest difference in active TB rates in British Columbia is that between employed and unemployed men [57]. Retired patients in Brazil were three times more likely to be infected with cluster-pattern strains than patients with any other occupation [58]. Occupations that have contact with infected cases (health care workers), those with silica exposure and silicosis (mining and construction), and low SES have higher TB mortality based upon National Center for Health Statistics data [59–61]. US TB case-fatality rates among unskilled white laborers were nearly seven times higher than among professional persons [62] and certain professions such as mining production are associated with elevated TB incidence rates [63]. Poor economic conditions such as self or even spousal unemployment are associated with greater health risks in general, including mortality, especially for those of working age [64].

Homelessness

The homeless have long been at increased risk of infection and progression to active TB due to a combination of poverty, poor nutrition, substance abuse, a lack of affordable housing, and increased exposure to public places [65, 66]. TB outbreaks among

the homeless are often attributed to lack of health insurance and treatment delay [67, 68]. As early as the late 1930s, focused X-ray screenings took place in poor populations, with 47,160 homeless men screened, 2250 (5.3 %) of whom were diagnosed with active tuberculosis; additionally 1919 (2.9 %) of 65,459 Harlem relief recipients were shown with active disease [69, 70]. In 1954, X-rays of almost 2000 men who were homeless revealed a detection rate of 4 %, or more than 15 times that of the general population [71]. In landmark studies in San Francisco, nearly tenfold higher infection levels were seen among homeless people with the TB case rate among African American and other non-white homeless people 3.5 times greater than among the general population [72]. In general, incidence rates among the homeless have been difficult to assess, given the lack of a true homeless census.

Based on a thorough homeless count, Feske et al. [73] have shown that more transient housing status is linked to TB incidence that is almost 100 times the US population average, with homelessness more closely associated with social determinants of health rather than disease comorbidities in multivariate analyses. Increased genotypic clustering, a surrogate for disease transmission, had also been associated with transient housing. Additionally, given lack of other transportation options, homeless persons with TB were more likely than nonhomeless to report weekly bus ridership. Buses and other forms of public transit have been shown to be effective means of TB transmission [74–77].

Evidence from Across the Globe

There is a strong association between higher TB incidence in countries and lower gross domestic product per capital [22]. National income levels per capita and income inequality are also important predictors for TB incidence and prevalence in Europe [78].

Within many countries, the distribution of TB has been shown to be higher among the poor than the nonpoor. In the Philippines, for example, the prevalence rate of smear-positive TB was found to be 1.6 times higher in urban poor communities than in nonpoor urban communities [79]. In China, 78 % of TB patients and their families were found to have per capita annual family income lower than the average for the locality [80]. The TB mortality rate in poor rural China was found to be nearly three times higher than that in more developed urban areas. A study in northern Vietnam observed that three times as many TB patients belonged to the lowest income quintile compared to those in the general study population [81].

While not explicitly testing the poverty–TB association, higher rates of TB in refugee camps worldwide have also indirectly demonstrated the role of social conditions on likelihood of acquiring disease. For example, in Kenya, the incidence of smear-positive TB was four times greater among refugee camp residents than for the local population [82].

Worse outcomes of disease have been noted recently in varying regions of the world among the poor. For example, in Ivanovo, Russia, TB case fatality rate (during

treatment) was higher among Russian Federation homeless patients than among other patients [83]. In Kenya, primarily female TB patients' major barrier to complying with treatment protocol was financial hardship [84]. The burden from losing a whole day's income to visit the clinic for medication resulted in lower compliance with the drug regimen.

Broader Social Structures

"Environmental" social determinants, such as housing conditions, social networks, and social support, are strong drivers of TB epidemics. Molecular tools have helped to discover complex social networks through which infection spreads [85–88]. High numbers of indoor contacts and intergenerational social mixing in households and transport likely contributed to high rates of TB transmission reported in a South African community [89]. Increasing numbers of social contacts occurred throughout childhood, adolescence, and young adulthood, predominantly in settings such as schools and public transport, paralleling the increasing TB infection rates during childhood and young adulthood reported in this community [90].

On the other hand, analyses reveal strong correlations between social capital and self-rated health on the aggregate level [91]. Social support mechanisms are instrumental in influencing health-seeking behavior, adherence, and TB patient well-being [92]. Indeed, social capital was strongly correlated with decreased TB case rates at the state level in the US [25]. Social networks can also positively influence adherence to TB drug therapy [93]. Similarly, in India, social infrastructure development which led to social capital generation was associated with decreasing TB incidence rates [94].

Physical Residential Infrastructure

Given its airborne transmission route, we would expect TB to predominate in indoor environments with less air exchange and poor ventilation. Indeed, in homes with poor natural ventilation in rural South Africa, estimated TB transmission risk was quite high [95]. Similarly, the possibility of an association between household ventilation (room volume, air change rates) and TB transmission has been examined in other studies [96, 97]. Evidence from healthcare facilities indicates that natural ventilation; that is, use of open doors and windows, greatly reduces the risk of airborne transmission [98]. In general, despite seeing disparities by ventilation, there is currently lack of sufficient data on the specification and quantification of minimum ventilation requirements in relation to the spread of airborne diseases [99].

While little work has taken place to examine the salutary effects of different housing designs on TB, housing designs intended to lower TB risks are now being implemented in the rebuilding of Haiti [100]. Factors that may inhibit increased

ventilation in a house include the outdoor temperature, noise, comfort, energy costs, the condition of windows or doors, or cultural and personal habits. A poorly ventilated home may suffer from high humidity and condensation, resulting in mold growth. Indeed, while not directly linked with TB infection, presence of mold may result in increased susceptibility to respiratory infection [101].

Links Between SES and Intermediary Risk Factors for TB

In addition to upstream determinants such as poverty, there is also increased awareness of the contribution of intermediary risk factors such as HIV, undernutrition, smoking, harmful use of alcohol, diabetes, and indoor air pollution to TB [102]. For example, children who had contact with index cases who were smokers showed a higher infection rate than those in contact with index cases who were nonsmokers [103]. These factors have all been linked to poverty, with strong associations documented at the individual level between these risk factors and poverty across medium- and low-income WHO-defined subregions [104] as well as in more urban areas of the US [105]. The population attributable fraction for TB in high-burden countries (which comprise 80 % of the global TB burden) for each of these risk factors has been estimated at between 8 and 27 % [102].

Inequities in Service Delivery

Poverty and low socioeconomic status are generally associated with worse treatment outcomes for those with TB [102] and differential access to care and health service delivery is specifically implicated in generating TB health outcome disparities, especially for the poorest and most vulnerable people [106, 107]. For example, TB patients in Georgia with lower household income were at greater risk of poor TB treatment outcomes [108]. Living in disadvantaged neighborhoods also reduces the likelihood of having a usual source of care and of obtaining recommended preventive services [109]. Limited access to care, in turn, including proximity, cost, service acceptability, and presence of public clinics and transportation, is likely to result in greater disease severity and transmission [110]. A recent systematic review showed that TB patients and households in sub-Saharan Africa often incurred costs of more than 10 % of their per capita income when utilizing TB treatment and care [111].

In a prospective cohort, longer patient delays, defined as the number of days from first TB symptoms to first medical visit specifically for those symptoms, were associated with nonwhite race and less education [112]. Longer healthcare delays, defined as days from first consultation to the initiation of treatment, were associated with presentation to a private physician or those receiving a different respiratory

illness diagnosis prior to TB diagnosis. Delay in diagnosis as well as total treatment delay was associated with greater transmission of infection to contacts among US-born participants [112, 113]. Delays due to missed diagnoses among HIV-coinfected TB patients have also been documented [114]. Low educational status, living in a more rural area, and limited availability of resources such as personal finances, health insurance, time, access to qualified health workers, and social support systems are a source of delay across the globe [115–117]. In the US, the proportion of advanced pulmonary TB increased the greatest in the last 15 years among whites, the employed, and the U.S. born, implying that low-incidence groups traditionally seen as being at low risk for TB disease were in fact receiving delayed diagnoses [118]. Additionally, individuals living in lower SES areas do not necessarily have more severe pulmonary disease at diagnosis [119].

Disparities Across Populations

Race and Ethnicity

The leading causes of death and disability have a disproportionate impact on African Americans, Alaska Natives, American Indians, Asian Americans, Hispanic Americans, and Pacific Islanders and TB is no exception [120]. Indeed, dating back to the 1930s, extensive study in the United States showed that low SES was an important contributor to increased risk of TB disease among blacks in the US [121]. In a survey impressive in its scope undertaken from 1931 to 1934, the authors found that the "economically more fortunate" Ballard Normal School African Americans had more rooms per home, fewer persons per room, more windows per room, and greater home ownership, than the general Macon, Georgia African American population. As well, this group had lower prevalence of TB, less history of contact in the household, and less positive history of TB in the family [121].

To this day, in the US, TB is largely a problem among both Hispanic and black populations, with rates eight to nine times that of white populations [122] (Fig. 11.3). At the zip-code level, Hispanics and African Americans have been shown to be exposed to risk factors such as poverty and crowded housing that may facilitate TB transmission [123]. The burden of pediatric TB is largely borne among the minority population in many parts of the US—heightened transmission among US-born non-Hispanic black adults results in subsequent infection of non-Hispanic black children [18]. Hispanic ethnicity and black race also independently predict clustering in molecular epidemiologic studies in the US [72, 124]. A recent molecular analysis found that younger age, fewer years of education, use of public transportation, and inner city residence were independently associated with black race among TB patients [125].

The disproportionate burden of TB among racial and ethnic groups is largely due to differences in living and social conditions [126]. For example, adjusting for six

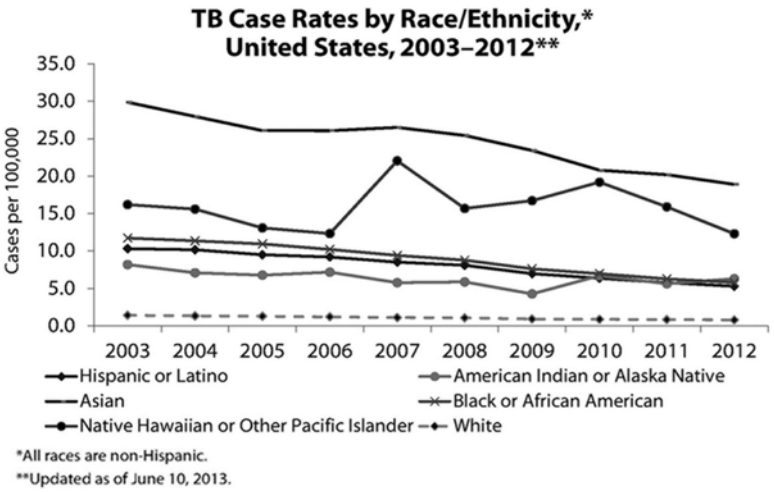

Fig. 11.3 TB case rates by race/ethnicity, United States, 2003–2012. *Source*: CDC. Reported Tuberculosis in the United States, 2012. Atlanta, GA: U.S. Department of Health and Human Services, CDC, October 2013

socioeconomic indicators, low SES accounted for approximately half of the increased risk for TB among blacks, Hispanics, and Native Americans [52]. TB risk factors such as HIV, substance abuse, and homelessness are not evenly distributed across racial groups and contribute to both increased exposure and progression from latent infection to active disease [125]. Racial minorities are also more likely to be uninsured, or to have other comorbidities, increasing barriers to health-care access [127].

Indigenous Peoples

There is an overall paucity of high-quality data, disaggregated surveillance data that would allow for the estimation of TB case rates in different groups. A recent systematic review found that indigenous peoples in high-, middle-, and low-income countries continue to bear a high and disproportionate burden of TB [128]. Groups most burdened by TB are located in small regions of Latin America, India, and Africa and in the US; TB case rates for American Indians are more than five times greater than for non-Hispanic white people and 13 times as great among Pacific Islanders [129]. Based on surveillance data, Native Americans and Alaska Natives were also more likely than other racial/ethnic groups to be homeless, excessively use alcohol, and come from places with a greater proportion of people living in poverty and without health insurance, all of which increase risk of TB disease.

Children

An estimated 11 % of all TB cases worldwide occur in children younger than age 15 years [130] with infection and disease acquisition common because of the high likelihood that children have frequent and close contact with adults with infectious TB. In high incidence communities, increased exposure to adults with pulmonary disease occurs to due to sociodemographic factors such as overcrowding.

The disproportionate degree to which children have TB often occurs because TB goes undetected. In most of the world, sputum microscopy is still the gold standard for TB diagnosis, yet young children generally are unable to produce a sputum sample, and if they do the sample may not be sufficient and often contains no detectable bacteria [131]. Providers thus often have to rely on clinical criteria, chest radiography, and skin testing alone [132]. Additionally, new drug development for treatment of children has lagged because of the difficulty of confirming active TB, concerns about adverse effects, complexities in involving children in drug development [133].

The WHO's "Towards Zero TB Deaths in Children" is advocating for viewing childhood TB in the context of a family illness, providing outreach to children with HIV, better integrating TB services with maternal and child health services, and actively reaching out and finding individuals with active TB [134]. Additionally, there has been a movement to include children in the picture when testing new rapid diagnostics and shorter, safer medication regimens that might actively benefit not only adults. Recent studies have shown that raising awareness about the risk of childhood TB among health workers and teaching them to use a scoring card for TB symptoms increases detection of childhood TB by almost three times [135]. Not only is poverty associated with increased risk of a child being exposed to TB, but it also influences risk of becoming infected and of then developing disease. Increased attention to childhood nutrition and improvement in the socioeconomic and environmental conditions of communities is likely to have a significant impact on new TB diagnoses and transmission to children [136].

Gender

Nearly twice as many men as women have been diagnosed with TB globally [137]. Men have higher mortality from TB, are at greater risk for treatment failure, and treatment default [138, 139]. Explanations for these imbalances have varied, with one hypothesis positing that gender-specific social roles may require men to have more social contact, thereby increasing TB exposure [140] and another differences in immunity due to levels of sex hormones that result in greater susceptibility among

men [141]. In most cases, the observed disparities in outcomes are not due to disparities in health care [142], although undernotification of women due to greater difficulties in gaining access to care may partly explain the disparity [143].

Disparities in Other Settings

The inmate population has been reported to have TB rates as much as 100 times higher than the civilian population [144]. One notable reason for the high rates of TB in correctional institutions is the greater proportion of persons who are at high risk for TB but who cannot access standard public health interventions such as universal HIV testing [145]. The fundamental relationship between SES and TB risk thus holds among vulnerable populations such as inmates [146]. Transmission risks particular to correctional institutions include close living quarters, poor ventilation, and overcrowding [147, 148]. Health disparities in treatment outcomes are particularly prevalent in this population. Inmates are much less likely to complete treatment [147]. This is a cause for concern both for the health of those individuals who did not receive a full course of curative therapy and for the communities in which they live. In Arkansas, it was discovered that the majority of persons (83 %) who later had TB had not received any TB screening while in jail [149]. A recent systematic review estimated the median estimated fraction of TB in the general population attributable to the exposure in prisons for TB as 8.5 % in high- and 6.3 % in middle/low-income countries [150].

Other High-Risk Populations

Patients in behavioral high-risk groups are likely to delay seeking timely medical care and not adhere to TB treatment, causing a prolonged period of infectivity and possible outbreaks [151–153]. Transmission among frequent alcohol or drug users may be common because of the inability or reluctance of patients to share information and behavioral patterns [87, 154].

Disparity by Place

TB rates vary highly by country and location, with the largest number of new TB cases occurring in Asia, accounting for 60 % of new cases globally, but highest incidence rates reported in sub-Saharan Africa, with over 255 cases per 100,000 population in 2012 [137]. In the U.S., great variation is also observed across the 50 states, from 0.4 cases per 100,000 (West Virginia) to nine cases per 100,000 (Alaska) in 2012 [155].

Urban and Rural Disparities

In large cities, tuberculosis mortality in both sexes has been shown to be three times higher in lowest than in the highest socioeconomic group among 35-year-olds and under, with a ratio of six to one among men over 35 [156]. A study in Denmark found that TB incidence rates in urban areas were twice as high as were incidence rates in rural areas [157] and TB in major cities has been shown to account for more than one-third of all US patients with TB [68]. Social conditions that affect urban areas such as homelessness, HIV, suboptimal access to healthcare, and migratory patterns are associated with higher TB incidence [158–160].

On the flip side, living in rural areas farther from available healthcare also matters. Individuals in indigenous First Nations communities who were more isolated and further removed from services had higher risks of incident TB [54]. Residents in rural China, Vietnam, Kenya, among many other settings, have shown low case-finding rates and high rates of TB disease and transmission [161–163].

The Role of Place: Spatial Analyses and Disparities

A number of studies have shown spatial clustering of TB cases, with significant associations of clustering found with social indices as well as unemployment, overcrowding, and income [30, 35, 36]. Similarly, areas that experienced the greatest child HIV/TB mortality were those without any health facility [164]. Uneven spatial distribution of cases has been documented in most continents [8, 165–167] and worldwide [168]. TB incidence in neighboring townships has even shown to have an effect on the TB incidence in a given township [169]. GIS-based screening based on multiple comorbidities, including TB, has been suggested as a tool to effectively penetrate populations with high disease burden and poor healthcare access [170]. Modeling studies have shown how high-incidence hotspots play an important role in propagating TB epidemics and the community- and city-wide impact in reducing the TB transmission rate in these hotspots [171].

Genotypic clusters of isolates often serve as surrogates for recently transmitted TB disease. A number of studies have found that molecular clusters occur in geographically distinct areas of communities and that they account for a high proportion of TB cases [172–175] (Fig. 11.4). Disparities in transmission are such that certain high transmission neighborhoods have been shown to overlap with areas of high incidence, and to include or exclude transmission across various population groups [172]. The combination of molecular and geographic tools has also been used to document community transmission of multidrug and extremely drug-resistant TB [176, 177].

In North America, groups at greatest risk for recent transmission appear to be men, persons born in the US or Canada, members of a minority race or ethnic group,

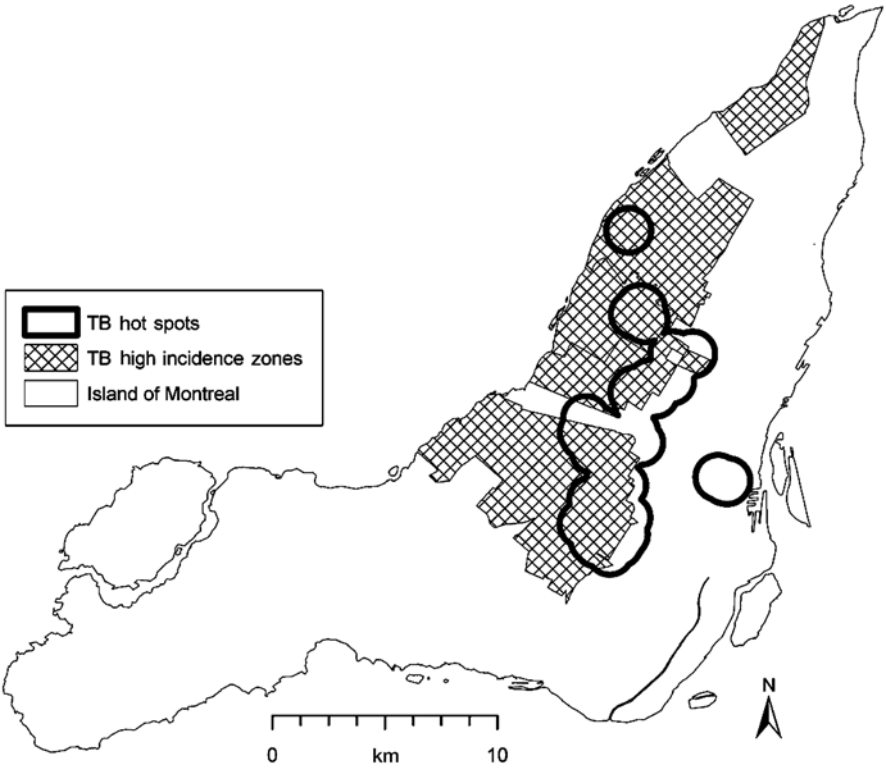

Fig. 11.4 Tuberculosis hot spots and high-incidence areas, Island of Montreal, 1996–2000. Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright The Union. Haase I, Olson S, Behr MA, et al. Use of geographic and genotyping tools to characterise tuberculosis transmission in Montreal. *The international journal of tuberculosis and lung disease*. Jun 2007;11(6):632-638

persons who abuse substances, and the homeless [174, 178–181]. Based on these findings, authors have advocated for location-based control efforts for the early identification of persons with latent TB infection and undiagnosed TB cases [173, 182–184].

The Role of Migration

Migrants are disproportionately affected by TB, often due to high TB incidence in their original hometown, and the limited access to healthcare and infrastructure both on their journey and destination, as well as poverty and social exclusion in their new home [185]. Language barriers and immigration status can be additional barriers to ameliorating TB disparities and inequality [22, 186]. Migrants from rural to urban

areas or across countries have delayed diagnoses that result in low treatment cure rates [187–189]. Since persons who were born in countries where TB prevalence is high might have acquired TB before immigrating [190], migrants may develop disease many years after arrival, mainly as a result of reactivation of latent tuberculosis [191]. Approximately half of new TB cases in the United States occur among foreign-born persons and the TB rate in foreign-born persons was approximately ten times that of persons born in the United States [4]. TB rates among foreign-born adolescents in the US were nearly 20 times as high as among US born [192]. An increase in the proportion of homeless who are foreign born has also been reported in Toronto, Canada [193].

Interestingly, in several settings in the US and Europe, it has been noted that disease from recent transmission of TB rarely exists among individuals born abroad but this is not true among the native-born population, where behavioral or social risk factors often predominate [194–196]. Additionally, low SES is only weakly associated with TB among foreign-born persons in the United States [197]. These findings support the hypothesis that TB rates among the foreign-born are more strongly influenced by experiences in their countries of origin than by their environments in their adopted country [198, 199]. Authors have suggested that future studies could explore the association of TB rates, SES, and country of birth based on differential immigrant settlement patterns [197].

National guidelines recommend that identification of local at-risk populations, increased knowledge of issues affecting immigrants and foreign-born persons, and modification of existing TB programs to meet the needs of these communities will help to reduce TB rates among foreign-born communities [4]. More broadly, the World Health Assembly stated that it is necessary "to formulate and implement strategies for improving the health of migrants" [200]. Blumberg has noted that in addition to focusing on the health needs of vulnerable migrant populations, the broader need is to invest in global tuberculosis control, and in development of better tools to enhance tuberculosis control [201].

Interventions

Rasanathan describes three types of interventions to address inequities and links between TB and other factors: health sector interventions, intersectoral policies impacting across society, and measurement and research [202]. In the health sector, strategies including health sector integration, health system improvement, and universal coverage can improve access to TB services, as well as lessen risk factors such as smoking and the harmful use of alcohol, which increase TB risk [203].

The WHO's Committee on Social Determinants of Health mentions a number of policies required across all sectors to reduce health inequities [20]. Specific social protection interventions, that provide social assistance and services to those in need, have been utilized among TB patients. Results from the Innovative Socioeconomic Interventions Against Tuberculosis (ISIAT) project suggest that social support leads

to large impacts on a variety of TB program outcomes, but that economic support has more limited impact [204]. In Brazil, the Bolsa Familia program providing conditional cash transfers to families has shown higher cure rates and use of DOTS among program participants [205]. However, in South Africa, economic support to patients in the form of vouchers did not significantly improve treatment outcomes [206]. Overall, there is a lack of studies on microfinance and cash transfer interventions that specifically address TB, though cash transfer and microfinance interventions can positively impact TB risk factors [207]. More recent slum upgrading strategies have not been studied with regard to TB outcomes [208]. Multifaceted strategies have been tried to combat the TB disparities seen among particular populations. In Seattle, a comprehensive 5-part screening approach controlled a large single-strain outbreak among the homeless [209]. New York's strategies of screening, increased surveillance, ultraviolet technologies, and nutritional focus have been effective in reducing the city's TB burden [210]. However, these strategies focus on the immediate TB burden and rarely examine the larger social determinants at hand.

Broad social interventions such as legislation against overcrowding at residential and industrial areas in some parts of Europe were factors which accounted for the decline of TB in the twentieth century [211]. In general, legislation and regulations serve toward a broader public health strategy for TB control [212].

Inequities in the health system are often mirrored in TB service delivery [213] and poor access impedes early and full case detection, and leads to low treatment success [214]. In general, measures to strengthen health systems seem to complement advances to control disease. For example, broader use of community health workers have been used to improve case detection and treatment success in Ethiopia [215] and Pakistan with the Lady Health Worker Programme [216]. In Thailand, broader health care access has been extended through the free primary health-care service package as part of the plan for universal health coverage, with particular targeting of metropolitan areas and highly vulnerable populations, including migrants [213]. Dean has recently mentioned the importance of shifting prevention programming to encompass a more diverse portfolio of prevention approaches [217, 218]. Increased investment in national TB programs has been shown to be significantly associated with a downward trend in the tuberculosis burden in the 22 WHO-defined--> high-burden countries [219]. A recent discussion has begun to consider the equity of health system performance throughout the continuum of care for TB [220].

Conclusion

Evidence of disparities in healthcare is remarkably consistent across a range of illnesses and healthcare services [221], with the disparities often rooted in the living and working conditions in the communities in which people live. Thus, as noted recently in various reports, it is the different social and economic living conditions that create large and predictable differences in health outcomes among nations and

between population groups within nations [222, 223]. Healthy People 2020s overarching framework explicitly states the importance of achieving health equity through the use of a systematic approach for addressing social determinants of health [224]. Examining service delivery synergies between existing poverty alleviation schemes and TB control efforts are key steps in this direction. Examining how to address social and structural barriers to TB disease prevention and control will likely hold the key to reducing disparities in TB health outcomes and in the eventual elimination of the disease.

Acknowledgments I would like to thank Lindsay Kohler, MPH, a doctoral student in Epidemiology at the University of Arizona's Mel and Enid Zuckerman College of Public Health, for her assistance in formatting, wordsmithing, and general support in writing this chapter.

References

1. Koh HK, Piotrowski JJ, Kumanyika S, Fielding JE. Healthy people: a 2020 vision for the social determinants approach. Health Educ Behav. 2011;38(6):551–7.
2. Woolf SH, Johnson RE, Fryer Jr GE, Rust G, Satcher D. The health impact of resolving racial disparities: an analysis of US mortality data. Am J Public Health. 2004;94(12):2078–81.
3. Millet JP, Moreno A, Fina L, et al. Factors that influence current tuberculosis epidemiology. Eur Spine J. 2013;22 Suppl 4:539–48.
4. Centers for Disease Control & Prevention. Trends in tuberculosis—United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(11):201–5.
5. Wanyeki I, Olson S, Brassard P, et al. Dwellings, crowding, and tuberculosis in Montreal. Soc Sci Med. 2006;63(2):501–11.
6. Kovesi T. Respiratory disease in Canadian First Nations and Inuit children. Paediatr Child Health. 2012;17(7):376–80.
7. Ukwaja KN, Alobu I, Nweke CO, Onyenwe EC. Healthcare-seeking behavior, treatment delays and its determinants among pulmonary tuberculosis patients in rural Nigeria: a cross-sectional study. BMC Health Serv Res. 2013;13:25.
8. Tadesse T, Demissie M, Berhane Y, Kebede Y, Abebe M. Long distance travelling and financial burdens discourage tuberculosis DOTs treatment initiation and compliance in Ethiopia: a qualitative study. BMC Public Health. 2013;13:424.
9. Pradhan A, Kielmann K, Gupte H, Bamne A, Porter JD, Rangan S. What 'outliers' tell us about missed opportunities for tuberculosis control: a cross-sectional study of patients in Mumbai, India. BMC Public Health. 2010;10:263.
10. Grigg ER. The arcana of tuberculosis with a brief epidemiologic history of the disease in the U.S.A. Am Rev Tuberc. 1958;78(2):151–72.
11. McKeown T. The role of medicine. Dream, mirage or nemesis? Oxford: Basil Blackwell; 1979.
12. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff. 2002;21(2):60–76.
13. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. Am J Public Health. 2010;100 Suppl 1:S186–96.
14. Minkler M, Fuller-Thomson E, Guralnik JM. Gradient of disability across the socioeconomic spectrum in the United States. N Engl J Med. 2006;355(7):695–703.
15. Engels F. The condition of the working class in England; 1842. (Henderson WO, Chaloner WH, New York, 1958, Transl.).

16. Lonnroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. Semin Respir Crit Care Med. 2008;29(5):481–91.
17. Jackson S, Sleigh AC, Wang GJ, Liu XL. Poverty and the economic effects of TB in rural China. Int J Tuberc Lung Dis. 2006;10(10):1104–10.
18. Stout JE, Saharia KK, Nageswaran S, Ahmed A, Hamilton CD. Racial and ethnic disparities in pediatric tuberculosis in North Carolina. Arch Pediatr Adolesc Med. 2006;160(6):631–7.
19. Hargreaves JR, Boccia D, Evans CA, Adato M, Petticrew M, Porter JD. The social determinants of tuberculosis: from evidence to action. Am J Public Health. 2011;101(4):654–62.
20. CSDH. 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: World Health Organization; 2008.
21. Dean HD, Fenton KA. Integrating a social determinants of health approach into public health practice: a five-year perspective of actions implemented by CDC's national center for HIV/AIDS, viral hepatitis, STD, and TB prevention. Public Health Rep. 2013;128 Suppl 3:5–11.
22. Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med. 2009;68(12):2240–6.
23. Blas E, Kurup AS. Equity, social determinants and public health programmes. Geneva: World Health Organization; 2010.
24. Lopez De Fede A, Stewart JE, Harris MJ, Mayfield-Smith K. Tuberculosis in socioeconomically deprived neighborhoods: missed opportunities for prevention. Int J Tuberc Lung Dis. 2008;12(12):1425–30.
25. Holtgrave D, Crosby R. Social determinants of tuberculosis case rates in the United States. Am J Prev Med. 2004;26(2):159–62.
26. Narayan-Parker D, Patel R. Voices of the poor: can anyone hear us? vol. 1. New York: World Bank Publications; 2000.
27. Klebs AC. Tuberculosis: a treatise by American authors on its etiology, pathology, frequency, semeiology, diagnosis, prognosis, prevention, and treatment. New York: D. Appleton; 1909.
28. Bureau NYCT. Tuberculosis in New York City, 1990. New York: New York City Department of Health; 1990.
29. Barr RG, Diez-Roux AV, Knirsch CA, Pablos-Mendez A. Neighborhood poverty and the resurgence of tuberculosis in New York City, 1984-1992. Am J Public Health. 2001;91(9):1487–93.
30. Oren E, Koepsell T, Leroux BG, Mayer J. Area-based socio-economic disadvantage and tuberculosis incidence. Int J Tuberc Lung Dis. 2012;16(7):880–5.
31. Krieger N, Waterman PD, Chen JT, Soobader MJ, Subramanian SV. Monitoring socioeconomic inequalities in sexually transmitted infections, tuberculosis, and violence: geocoding and choice of area-based socioeconomic measures—the public health disparities geocoding project (US). Public Health Rep. 2003;118(3):240–60.
32. Parslow R, El-Shimy NA, Cundall DB, McKinney PA. Tuberculosis, deprivation, and ethnicity in Leeds, UK, 1982-1997. Arch Dis Child. 2001;84(2):109–13.
33. Spence DP, Hotchkiss J, Williams CS, Davies PD. Tuberculosis and poverty. BMJ. 1993;307(6907):759–61.
34. Tocque K, Regan M, Remmington T, et al. Social factors associated with increases in tuberculosis notifications. Eur Respir J. 1999;13(3):541–5.
35. Munch Z, Van Lill SW, Booysen CN, Zietsman HL, Enarson DA, Beyers N. Tuberculosis transmission patterns in a high-incidence area: a spatial analysis. Int J Tuberc Lung Dis. 2003;7(3):271–7.
36. Souza WV, Ximenes R, Albuquerque MF, et al. The use of socioeconomic factors in mapping tuberculosis risk areas in a city of northeastern Brazil. Rev Panam Salud Publica. 2000;8(6):403–10.
37. de Alencar Ximenes RA, de Fatima Pessoa Militao de Albuquerque M, Souza WV, et al. Is it better to be rich in a poor area or poor in a rich area? A multilevel analysis of a case-control study of social determinants of tuberculosis. Int J Epidemiol. 2009;38(5):1285–96.

38. Harling G, Ehrlich R, Myer L. The social epidemiology of tuberculosis in South Africa: a multilevel analysis. Soc Sci Med. 2008;66(2):492–505.
39. Alvarez-Hernandez G, Lara-Valencia F, Reyes-Castro PA, Rascon-Pacheco RA. An analysis of spatial and socio-economic determinants of tuberculosis in Hermosillo, Mexico, 2000-2006. Int J Tuberc Lung Dis. 2010;14(6):708–13.
40. Odone A, Ricco M, Morandi M, Borrini BM, Pasquarella C, Signorelli C. Epidemiology of tuberculosis in a low-incidence Italian region with high immigration rates: differences between not Italy-born and Italy-born TB cases. BMC Public Health. 2011;11:376.
41. Boccia D, Hargreaves J, De Stavola BL, et al. The association between household socioeconomic position and prevalent tuberculosis in Zambia: a case-control study. PLoS One. 2011;6(6), e20824.
42. Gustafson P, Gomes VF, Vieira CS, et al. Tuberculosis in Bissau: incidence and risk factors in an urban community in sub-Saharan Africa. Int J Epidemiol. 2004;33(1):163–72.
43. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis. 2006;10(1):80–6.
44. Bensenor IM, Lotufo PA. Household income, sex and respiratory mortality in Sao Paulo, Brazil, 1996-2010. Int J Tuberc Lung Dis. 2012;16(12):1692–8.
45. Engel A, Roberts J. Tuberculin skin test reaction among adults 25-74 years, United States, 1971-72. Vital Health Stat 11. 1977;(204):1–40. Data from the National Health Survey.
46. Reichman LB, O'Day R. Tuberculous infection in a large urban population. Am Rev Respir Dis. 1978;117(4):705–12.
47. Lienhardt C, Fielding K, Sillah J, et al. Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in the Gambia. Am J Respir Crit Care Med. 2003;168(4):448–55.
48. Claessens NJ, Gausi FF, Meijnen S, Weismuller MM, Salaniponi FM, Harries AD. High frequency of tuberculosis in households of index TB patients. Int J Tuberc Lung Dis. 2002;6(3):266–9.
49. Boccia D, Hargreaves J, Ayles H, Fielding K, Simwinga M, Godfrey-Faussett P. Tuberculosis infection in Zambia: the association with relative wealth. Am J Trop Med Hyg. 2009;80(6):1004–11.
50. Vynnycky E, Fine PE. Interpreting the decline in tuberculosis: the role of secular trends in effective contact. Int J Epidemiol. 1999;28(2):327–34.
51. Baker M, Das D, Venugopal K, Howden-Chapman P. Tuberculosis associated with household crowding in a developed country. J Epidemiol Community Health. 2008;62(8):715–21.
52. Cantwell MF, McKenna MT, McCray E, Onorato IM. Tuberculosis and race/ethnicity in the United States: impact of socioeconomic status. Am J Respir Crit Care Med. 1998;157(4 Pt 1):1016–20.
53. Drucker E, Alcabes P, Bosworth W, Sckell B. Childhood tuberculosis in the Bronx, New York. Lancet. 1994;343(8911):1482–5.
54. Clark M, Riben P, Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. Int J Epidemiol. 2002;31(5):940–5.
55. Myers W, Westenhouse J, Flood J, Riley L. An ecological study of tuberculosis transmission in California. Am J Public Health. 2006;96(4):685–90.
56. Ladefoged K, Rendal T, Skifte T, Andersson M, Soborg B, Koch A. Risk factors for tuberculosis in Greenland: case-control study. Int J Tuberc Lung Dis. 2011;15(1):44–9.
57. Enarson DA, Wang JS, Dirks JM. The incidence of active tuberculosis in a large urban area. Am J Epidemiol. 1989;129(6):1268–76.
58. Cafrune PI, Riley LW, Possuelo LG, et al. Recent transmission of tuberculosis involving retired patients. J Infect. 2006;53(6):370–6.
59. Bang KM, Weissman DN, Wood JM, Attfield MD. Tuberculosis mortality by industry in the United States, 1990-1999. Int J Tuberc Lung Dis. 2005;9(4):437–42.
60. Centers for Disease Control and Prevention. Proportionate mortality from pulmonary tuberculosis associated with occupations—28 states, 1979-1990. MMWR Morb Mortal Wkly Rep. 1995;44(1):14–9.

61. Nasrullah M, Mazurek JM, Wood JM, Bang KM, Kreiss K. Silicosis mortality with respiratory tuberculosis in the United States, 1968-2006. Am J Epidemiol. 2011;174(7):839–48.
62. Farmer P. Infections and inequalities: the modern plagues. Berkeley: University of California; 2001.
63. Stuckler D, Basu S, McKee M, Lurie M. Mining and risk of tuberculosis in sub-Saharan Africa. Am J Public Health. 2011;101(3):524–30.
64. Halliday TJ. Unemployment and mortality: evidence from the PSID. Soc Sci Med. 2014;113C:15–22.
65. Story A, Murad S, Roberts W, Verheyen M, Hayward AC, London Tuberculosis Nurses Network. Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax. 2007;62(8):667–71.
66. Reid A, Heyworth J, de Klerk N, Musk AW. The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. Occup Environ Med. 2008;65(11):743–9.
67. Bierman AS, Dunn JR. Swimming upstream. Access, health outcomes, and the social determinants of health. J Gen Intern Med. 2006;21(1):99–100.
68. Oren E, Winston CA, Pratt R, Robison VA, Narita M. Epidemiology of urban tuberculosis in the United States, 2000-2007. Am J Public Health. 2011;101(7):1256–63.
69. Edwards H. Tuberculosis case finding. Studies in mass surveys. Introduction and general summary. Am Rev Tuberc. 1940;41:3–7.
70. Downes J, Connell H. Case-finding among Puerto Ricans in New York City. Am Rev Tuberc. 1940;41:131–9.
71. Lowell A. Socio-economic conditions and tuberculosis prevalence, New York City, 1949-1951. New York: New York Tuberculosis and Health Association; 1956.
72. Small P, Hopewell P, Singh S, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. N Engl J Med. 1994;330(24):1703–9.
73. Feske ML, Teeter LD, Musser JM, Graviss EA. Counting the homeless: a previously incalculable tuberculosis risk and its social determinants. Am J Public Health. 2013;103(5):839–48.
74. Yusuf HR, Braden CR, Greenberg AJ, Weltman AC, Onorato IM, Valway SE. Tuberculosis transmission among five school bus drivers and students in two New York counties. Pediatrics. 1997;100(3), E9.
75. Feske ML, Teeter LD, Musser JM, Graviss EA. Giving TB wheels: public transportation as a risk factor for tuberculosis transmission. Tuberculosis. 2011;91 Suppl 1:S16–23.
76. Andrews JR, Morrow C, Wood R. Modeling the role of public transportation in sustaining tuberculosis transmission in South Africa. Am J Epidemiol. 2013;177(6):556–61.
77. Tan de Bibiana J, Rossi C, Rivest P, et al. Tuberculosis and homelessness in Montreal: a retrospective cohort study. BMC Public Health. 2011;11:833.
78. Ploubidis GB, Palmer MJ, Blackmore C, et al. Social determinants of tuberculosis in Europe: a prospective ecological study. Eur Respir J. 2012;40(4):925–30.
79. Tupasi T, Radhakrishna S, Quelapio M, et al. Tuberculosis in the urban poor settlements in the Philippines. Int J Tuberc Lung Dis. 2000;4(1):4–11.
80. Xu B. Does tuberculosis care reach the poor? A study of TB control programmes in two counties in rural China; 2003.
81. Thorson A, Hoa N, Long N, Allebeck P, Diwan V. Do women with tuberculosis have a lower likelihood of getting diagnosed? Prevalence and case detection of sputum smear positive pulmonary TB, a population-based study from Vietnam. J Clin Epidemiol. 2004;57(4):398–402.
82. Githui W, Hawken M, Juma E, et al. Surveillance of drug-resistant tuberculosis and molecular evaluation of transmission of resistant strains in refugee and non-refugee populations in North-Eastern Kenya. Int J Tuberc Lung Dis. 2000;4(10):947–55.
83. Keshavjee S, Gelmanova I, Pasechnikov A, et al. Treating multidrug-resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. Ann N Y Acad Sci. 2008;1136:1–11.

84. Ellis A, Gogel R, Roman B, Watson J, Indyk D, Rosenberg G. The STARK study: a cross-sectional study of adherence to short-term drug regiments in urban Kenya. Soc Work Health Care. 2006;42(3–4):237–50.
85. Klovdahl AS, Graviss EA, Yaganehdoost A, et al. Networks and tuberculosis: an undetected community outbreak involving public places. Soc Sci Med. 2001;52(5):681–94.
86. McElroy PD, Rothenberg RB, Varghese R, et al. A network-informed approach to investigating a tuberculosis outbreak: implications for enhancing contact investigations. Int J Tuberc Lung Dis. 2003;7(12 Suppl 3):S486–93.
87. Sterling TR. Report from the 38th IDSA: tuberculosis & HIV. Hopkins HIV Rep. 2000;12(5):2.
88. Andre M, Ijaz K, Tillinghast JD, et al. Transmission network analysis to complement routine tuberculosis contact investigations. Am J Public Health. 2007;97(3):470–7.
89. Johnstone-Robertson SP, Mark D, Morrow C, et al. Social mixing patterns within a South African township community: implications for respiratory disease transmission and control. Am J Epidemiol. 2011;174(11):1246–55.
90. Wood R, Racow K, Bekker LG, et al. Indoor social networks in a South African township: potential contribution of location to tuberculosis transmission. PLoS One. 2012;7(6), e39246.
91. von dem Knesebeck O, Verde PE, Dragano N. Education and health in 22 European countries. Soc Sci Med. 2006;63(5):1344–51.
92. Paz-Soldan VA, Alban RE, Jones CD, Oberhelman RA. The provision of and need for social support among adult and pediatric patients with tuberculosis in Lima, Peru: a qualitative study. BMC Health Serv Res. 2013;13:290.
93. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. Am Rev Respir Dis. 1993;147(5):1311–20.
94. Chandra S, Sharma N, Joshi K, Aggarwal N, Kannan AT. Resurrecting social infrastructure as a determinant of urban tuberculosis control in Delhi, India. Health Res Policy Syst. 2014;12(1):3.
95. Lygizos M, Shenoi SV, Brooks RP, et al. Natural ventilation reduces high TB transmission risk in traditional homes in rural KwaZulu-Natal, South Africa. BMC Infect Dis. 2013;13:300.
96. Chamie G, Wandera B, Luetkemeyer A, et al. Household ventilation and tuberculosis transmission in Kampala, Uganda. Int J Tuberc Lung Dis. 2013;17(6):764–70.
97. Beggs CB, Noakes CJ, Sleigh PA, Fletcher LA, Siddiqi K. The transmission of tuberculosis in confined spaces: an analytical review of alternative epidemiological models. Int J Tuberc Lung Dis. 2003;7(11):1015–26.
98. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med. 2007;4(2), e68.
99. Li Y, Leung GM, Tang JW, et al. Role of ventilation in airborne transmission of infectious agents in the built environment - a multidisciplinary systematic review. Indoor Air. 2007;17(1):2–18.
100. ARCHIVE Global. Housing and health in Haiti. 2014. http://www.archiveglobal.org/our-work-6/haiti-3/. Accessed 17 Feb 2014.
101. Dales RE, Zwanenburg H, Burnett R, Franklin CA. Respiratory health effects of home dampness and molds among Canadian children. Am J Epidemiol. 1991;134(2):196–203.
102. Lonnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet. 2010;375(9728):1814–29.
103. Singh M, Mynak ML, Kumar L, Mathew JL, Jindal SK. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child. 2005;90(6):624–8.
104. Blakely T, Hales S, Kieft C, Wilson N, Woodward A. The global distribution of risk factors by poverty level. Bull World Health Organ. 2005;83(2):118–26.
105. Vaughan AS, Rosenberg E, Shouse RL, Sullivan PS. Connecting race and place: a county-level analysis of White, Black, and Hispanic HIV prevalence, poverty, and level of urbanization. Am J Public Health. 2014;104:e77–84.
106. Reichman LB, Hershfield ES. Tuberculosis: a comprehensive international approach. New York: Marcel Dekker; 2000.

107. Asch S, Leake B, Gelberg L. Does fear of immigration authorities deter tuberculosis patients from seeking care? West J Med. 1994;161(4):373–6.
108. Djibuti M, Mirvelashvili E, Makharashvili N, Magee MJ. Household income and poor treatment outcome among patients with tuberculosis in Georgia: a cohort study. BMC Public Health. 2014;14(1):88.
109. Kirby JB, Kaneda T. Neighborhood socioeconomic disadvantage and access to health care. J Health Soc Behav. 2005;46(1):15–31.
110. Benjamins MR, Kirby JB, Bond Huie SA. County characteristics and racial and ethnic disparities in the use of preventive services. Prev Med. 2004;39(4):704–12.
111. Barter DM, Agboola SO, Murray MB, Barnighausen T. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa--a systematic review. BMC Public Health. 2012;12:980.
112. Golub J, Bur S, Cronin W, et al. Patient and health care system delays in pulmonary tuberculosis diagnosis in a low-incidence state. Int J Tuberc Lung Dis. 2005;9(9):992–8.
113. Golub J, Bur S, Cronin W, et al. Delayed tuberculosis diagnosis and tuberculosis transmission. Int J Tuberc Lung Dis. 2006;10(1):24–30.
114. Coimbra I, Maruza M, Militao-Albuquerque Mde F, et al. Associated factors for treatment delay in pulmonary tuberculosis in HIV-infected individuals: a nested case-control study. BMC Infect Dis. 2012;12:208.
115. Li Y, Ehiri J, Tang S, et al. Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. BMC Med. 2013;11:156.
116. Hussen A, Biadgilign S, Tessema F, Mohammed S, Deribe K, Deribew A. Treatment delay among pulmonary tuberculosis patients in pastoralist communities in Bale Zone, Southeast Ethiopia. BMC Res Notes. 2012;5:320.
117. Kiwuwa M, Charles K, Harriet M. Patient and health service delay in pulmonary tuberculosis patients attending a referral hospital: a cross-sectional study. BMC Public Health. 2005;5:122.
118. Wallace R, Kammerer J, Iademarco M, Althomsons S, Winston C, Navin T. Increasing proportions of advanced pulmonary tuberculosis reported in the United States: are delays in diagnosis on the rise? Am J Respir Crit Care Med. 2009;180(10):1016–22.
119. Oren E, Narita M, Nolan C, Mayer J. Area-level socioeconomic disadvantage and severe pulmonary tuberculosis: U.S., 2000-2008. Public Health Rep. 2013;128(2):99–109.
120. Liburd LC, Giles HW, Mensah GA. Looking through a glass, darkly: eliminating health disparities. Prev Chronic Dis. 2006;3(3):A72.
121. Williams G, Applewhite J. Tuberculosis in the Negroes of Georgia: economic, racial and constitutional aspects. Am J Hyg. 1939;29:61–109.
122. Centers for Disease Control & Prevention. Trends in tuberculosis—United States, 2011. MMWR Morb Mortal Wkly Rep. 2012;61(11):181–5.
123. Acevedo-Garcia D. Zip code-level risk factors for tuberculosis: neighborhood environment and residential segregation in New Jersey, 1985-1992. Am J Public Health. 2001;91(5):734–41.
124. El Sahly HM, Adams GJ, Soini H, Teeter L, Musser JM, Graviss EA. Epidemiologic differences between United States- and foreign-born tuberculosis patients in Houston, Texas. J Infect Dis. 2001;183(3):461–8.
125. Serpa JA, Teeter LD, Musser JM, Graviss EA. Tuberculosis disparity between US-born blacks and whites, Houston, Texas, USA. Emerg Infect Dis. 2009;15(6):899–904.
126. AHRQ. National healthcare disparities report. 2010. http://www.ahrq.gov/research/findings/nhqrdr/nhdr10/Ackno.html.
127. AHRQ. National healthcare disparities report. 2006. http://archive.ahrq.gov/qual/nhdr06/nhdr06.htm.
128. Tollefson D, Bloss E, Fanning A, Redd JT, Barker K, McCray E. Burden of tuberculosis in indigenous peoples globally: a systematic review. Int J Tuberc Lung Dis. 2013;17(9):1139–50.

129. Bloss E, Holtz TH, Jereb J, et al. TB in indigenous peoples in the US, 2003-2008. Public Health Rep. 2011;126:677–89.
130. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis. 2004;8(5):636–47.
131. Marais BJ, Graham SM, Cotton MF, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. J Infect Dis. 2007;196 Suppl 1:S76–85.
132. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Stop TB Department; Department of HIV/AIDS; 2007.
133. Burman W, McNeeley D, Moulton LH, Spigelman M, Vernon A. Advancing the science in clinical trials for new TB drugs. Int J Tuberc Lung Dis. 2008;12(2):111–2.
134. Raviglione M, Zumla A, Marais B, Horton R, Motsoaledi A. A sustainable agenda for tuberculosis control and research. Lancet. 2012;379(9821):1077–8.
135. Talukder K, Salim MA, Jerin I, et al. Intervention to increase detection of childhood tuberculosis in Bangladesh. Int J Tuberc Lung Dis. 2012;16(1):70–5.
136. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clin Infect Dis. 2010;50 Suppl 3:S184–94.
137. World Health Organization. Global tuberculosis report 2013. Geneva: World Health Organization; 2013.
138. Feng JY, Huang SF, Ting WY, et al. Gender differences in treatment outcomes of tuberculosis patients in Taiwan: a prospective observational study. Clin Microbiol Infect. 2012;18(9):E331–7.
139. Balasubramanian R, Garg R, Santha T, et al. Gender disparities in tuberculosis: report from a rural DOTS programme in south India. Int J Tuberc Lung Dis. 2004;8(3):323–32.
140. Vlassoff C, Moreno CG. Placing gender at the centre of health programming: challenges and limitations. Soc Sci Med. 2002;54(11):1713–23.
141. Neyrolles O, Quintana-Murci L. Sexual inequality in tuberculosis. PLoS Med. 2009;6(12), e1000199.
142. Borgdorff MW, Behr MA, Nagelkerke NJ, Hopewell PC, Small PM. Transmission of tuberculosis in San Francisco and its association with immigration and ethnicity. Int J Tuberc Lung Dis. 2000;4(4):287–94.
143. Weiss MG, Sommerfeld J, Uplekar MW. Social and cultural dimensions of gender and tuberculosis. Int J Tuberc Lung Dis. 2008;12(7):829–30.
144. World Health Organization. Tuberculosis control in prisons: a manual for programme managers. Geneva: WHO; 2000.
145. Hammett TM. 1996–1997 Update:HIV/AIDS, STDs, and TB in correctional facilities. Issues and practices in criminal justice. Washington, DC: US Department of Justice, National Institute of Justice; 1999.
146. Kim S, Crittenden KS. Risk factors for tuberculosis among inmates: a retrospective analysis. Public Health Nurs. 2005;22(2):108–18.
147. MacNeil JR, Lobato MN, Moore M. An unanswered health disparity: tuberculosis among correctional inmates, 1993 through 2003. Am J Public Health. 2005;95(10):1800–5.
148. White MC, Tulsky JP, Portillo CJ, Menendez E, Cruz E, Goldenson J. Tuberculosis prevalence in an urban jail: 1994 and 1998. Int J Tuberc Lung Dis. 2001;5(5):400–4.
149. Chaves F, Dronda F, Cave MD, et al. A longitudinal study of transmission of tuberculosis in a large prison population. Am J Respir Crit Care Med. 1997;155(2):719–25.
150. Baussano I, Williams BG, Nunn P, Beggiato M, Fedeli U, Scano F. Tuberculosis incidence in prisons: a systematic review. PLoS Med. 2010;7(12), e1000381.
151. Perlman DC, Salomon N, Perkins MP, Yancovitz S, Paone D, Des Jarlais DC. Tuberculosis in drug users. Clin Infect Dis. 1995;21(5):1253–64.
152. Chin DP, Cummings KC, Sciortino S, et al. Progress and problems in achieving the United States national target for completion of antituberculosis treatment. Int J Tuberc Lung Dis. 2000;4(8):744–51.

153. Oeltmann J, Kammerer J, Pevzner E, Moonan P. Tuberculosis and substance abuse in the United States, 1997-2006. Arch Intern Med. 2009;169(2):189–97.
154. Malakmadze N, Gonzalez IM, Oemig T, et al. Unsuspected recent transmission of tuberculosis among high-risk groups: implications of universal tuberculosis genotyping in its detection. Clin Infect Dis. 2005;40(3):366–73.
155. CDC. Reported tuberculosis in the United States, 2012. Atlanta: U.S. Department of Health and Human Services; 2013.
156. Rieder H, Cauthen G, Kelly G, Bloch A, Snider DJ. Tuberculosis in the United States. JAMA. 1989;262(3):385–9.
157. Horwitz O, Knudsen J. A follow-up study of tuberculosis incidence and general mortality in various occupational-social groups of the Danish population. Bull World Health Organ. 1961;24:793–805.
158. Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community-based directly observed therapy for tuberculosis. JAMA. 1995;274(12):945–51.
159. Brudney K, Dobkin J. Resurgent tuberculosis in New York City. Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. Am Rev Respir Dis. 1991;144(4):745–9.
160. Rose III RC, McGowan Jr JE. Urban tuberculosis: some modern problems. Am J Med Sci. 1984;287(1):24–6.
161. Chen W, Shu W, Wang M, et al. Pulmonary tuberculosis incidence and risk factors in rural areas of China: a cohort study. PLoS One. 2013;8(3), e58171.
162. Buu TN, van Soolingen D, Huyen MN, et al. Tuberculosis acquired outside of households, rural Vietnam. Emerg Infect Dis. 2010;16(9):1466–8.
163. Van't Hoog AH, Marston BJ, Ayisi JG, et al. Risk factors for inadequate TB case finding in Rural Western Kenya: a comparison of actively and passively identified TB patients. PLoS One. 2013;8(4), e61162.
164. Musenge E, Vounatsou P, Collinson M, Tollman S, Kahn K. The contribution of spatial analysis to understanding HIV/TB mortality in children: a structural equation modelling approach. Glob Health Action. 2013;6:19266.
165. Wang T, Xue F, Chen Y, Ma Y, Liu Y. The spatial epidemiology of tuberculosis in Linyi City, China, 2005-2010. BMC Public Health. 2012;12:885.
166. Lin H, Shin S, Blaya JA, et al. Assessing spatiotemporal patterns of multidrug-resistant and drug-sensitive tuberculosis in a South American setting. Epidemiol Infect. 2011;139(11): 1784–93.
167. Tiwari N, Adhikari CM, Tewari A, Kandpal V. Investigation of geo-spatial hotspots for the occurrence of tuberculosis in Almora district, India, using GIS and spatial scan statistic. Int J Health Geogr. 2006;5:33.
168. Liu Y, Jiang S, Liu Y, et al. Spatial epidemiology and spatial ecology study of worldwide drug-resistant tuberculosis. Int J Health Geogr. 2011;10:50.
169. Ng IC, Wen TH, Wang JY, Fang CT. Spatial dependency of tuberculosis incidence in Taiwan. PLoS One. 2012;7(11), e50740.
170. Goswami ND, Hecker EJ, Vickery C, et al. Geographic information system-based screening for TB, HIV, and syphilis (GIS-THIS): a cross-sectional study. PLoS One. 2012;7(10), e46029.
171. Dowdy DW, Golub JE, Chaisson RE, Saraceni V. Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. Proc Natl Acad Sci U S A. 2012;109(24):9557–62.
172. Haase I, Olson S, Behr MA, et al. Use of geographic and genotyping tools to characterise tuberculosis transmission in Montreal. Int J Tuberc Lung Dis. 2007;11(6):632–8.
173. Bishai W, Graham N, Harrington S, et al. Molecular and geographic patterns of tuberculosis transmission after 15 years of directly observed therapy. JAMA. 1998;280(19):1679–84.
174. Moonan PK, Ghosh S, Oeltmann JE, Kammerer JS, Cowan LS, Navin TR. Using genotyping and geospatial scanning to estimate recent mycobacterium tuberculosis transmission, United States. Emerg Infect Dis. 2012;18(3):458–65.

175. Easterbrook PJ, Gibson A, Murad S, et al. High rates of clustering of strains causing tuberculosis in Harare, Zimbabwe: a molecular epidemiological study. J Clin Microbiol. 2004;42(10):4536–44.
176. Murase Y, Maeda S, Yamada H, et al. Clonal expansion of multidrug-resistant and extensively drug-resistant tuberculosis, Japan. Emerg Infect Dis. 2010;16(6):948–54.
177. Chihota VN, Muller B, Mlambo CK, et al. Population structure of multi- and extensively drug-resistant Mycobacterium tuberculosis strains in South Africa. J Clin Microbiol. 2012;50(3):995–1002.
178. Driver C, Kreiswirth B, Macaraig M, et al. Molecular epidemiology of tuberculosis after declining incidence, New York City, 2001-2003. Epidemiol Infect. 2007;135(4):634–43.
179. Fok A, Numata Y, Schulzer M, FitzGerald M. Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies. Int J Tuberc Lung Dis. 2008;12(5):480–92.
180. Rossi C, Zwerling A, Thibert L, et al. Mycobacterium tuberculosis transmission over an 11-year period in a low-incidence, urban setting. Int J Tuberc Lung Dis. 2012;16(3):312–8.
181. Tuite AR, Guthrie JL, Alexander DC, et al. Epidemiological evaluation of spatiotemporal and genotypic clustering of Mycobacterium tuberculosis in Ontario, Canada. Int J Tuberc Lung Dis. 2013;17(10):1322–7.
182. Moonan PK, Bayona M, Quitugua TN, et al. Using GIS technology to identify areas of tuberculosis transmission and incidence. Int J Health Geogr. 2004;3(1):23.
183. Oppong JR, Mikler AR, Moonan P, Weis S. From medical geography to computational epidemiology–dynamics of tuberculosis transmission in enclosed spaces. Innovative Internet Community Systems. New York: Springer; 2006. p. 189–97.
184. Cook VJ, Shah L, Gardy J, Bourgeois AC. Recommendations on modern contact investigation methods for enhancing tuberculosis control. Int J Tuberc Lung Dis. 2012;16(3): 297–305.
185. Hargreaves S, Carballo M, Friedland JS. Screening migrants for tuberculosis: where next? Lancet Infect Dis. 2009;9(3):139–40.
186. Juckett G. Caring for Latino patients. Am Fam Physician. 2013;87(1):48–54.
187. Zhang LX, Tu DH, An YS, Enarson DA. The impact of migrants on the epidemiology of tuberculosis in Beijing, China. Int J Tuberc Lung Dis. 2006;10(9):959–62.
188. Shen X, Xia Z, Li X, et al. Tuberculosis in an urban area in China: differences between urban migrants and local residents. PLoS One. 2012;7(11), e51133.
189. Mor Z, Kolb H, Lidji M, Migliori G, Leventhal A. Tuberculosis diagnostic delay and therapy outcomes of non-national migrants in Tel Aviv, 1998-2008. Euro Surveill. 2013;18(12).
190. Pottie K, Janakiram P, Topp P, McCarthy A. Prevalence of selected preventable and treatable diseases among government-assisted refugees: implications for primary care providers. Can Fam Physician. 2007;53(11):1928–34.
191. Cain KP, Benoit SR, Winston CA, Mac Kenzie WR. Tuberculosis among foreign-born persons in the United States. JAMA. 2008;300(4):405–12.
192. Menzies HJ, Winston CA, Holtz TH, Cain KP, Mac Kenzie WR. Epidemiology of tuberculosis among US- and foreign-born children and adolescents in the United States, 1994-2007. Am J Public Health. 2010;100(9):1724–9.
193. Khan K, Rea E, McDermaid C, et al. Active tuberculosis among homeless persons, Toronto, Ontario, Canada, 1998-2007. Emerg Infect Dis. 2011;17(3):357–65.
194. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in U.S.-born and foreign-born persons. Am J Respir Crit Care Med. 1998;158(6):1797–803.
195. Vanhomwegen J, Kwara A, Martin M, et al. Impact of immigration on the molecular epidemiology of tuberculosis in Rhode Island. J Clin Microbiol. 2011;49(3):834–44.
196. Inigo J, Garcia de Viedma D, Arce A, et al. Analysis of changes in recent tuberculosis transmission patterns after a sharp increase in immigration. J Clin Microbiol. 2007;45(1):63–9.

197. Olson NA, Davidow AL, Winston CA, Chen MP, Gazmararian JA, Katz DJ. A national study of socioeconomic status and tuberculosis rates by country of birth, United States, 1996-2005. BMC Public Health. 2012;12:365.
198. Geng E, Kreiswirth B, Driver C, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. N Engl J Med. 2002;346(19):1453–8.
199. Cain KP, Haley CA, Armstrong LR, et al. Tuberculosis among foreign-born persons in the United States: achieving tuberculosis elimination. Am J Respir Crit Care Med. 2007;175(1):75–9.
200. World Health Assembly. Health of migrants; 2010.
201. Blumberg HM, Migliori GB, Ponomarenko O, Heldal E. Tuberculosis on the move. Lancet. 2010;375(9732):2127–9.
202. Rasanathan K, Sivasankara Kurup A, Jaramillo E, Lonnroth K. The social determinants of health: key to global tuberculosis control. Int J Tuberc Lung Dis. 2011;15 Suppl 2:S30–6.
203. World Health Organization. Everybody business : strengthening health systems to improve health outcomes: WHO's framework for action. Geneva: WHO; 2007.
204. Rocha C, Montoya R, Zevallos K, et al. The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. Int J Tuberc Lung Dis. 2011;15 Suppl 2:S50–7.
205. Barreira D. Social protection interventions for TB control. The Brazilian Experience. 2013. http://www.who.int/tb/barreira_brazilexperience.pdf. Accessed 2014
206. Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials. 2013;14:154.
207. Boccia D, Hargreaves J, Lonnroth K, et al. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications. Int J Tuberc Lung Dis. 2011;15 Suppl 2:S37–49.
208. Turley R, Saith R, Bhan N, Rehfuess E, Carter B. Slum upgrading strategies involving physical environment and infrastructure interventions and their effects on health and socio-economic outcomes. Cochrane Database Syst Rev. 2013;(1):CD010067.
209. Lofy KH, McElroy PD, Lake L, et al. Outbreak of tuberculosis in a homeless population involving multiple sites of transmission. Int J Tuberc Lung Dis. 2006;10(6):683–9.
210. McAdam JM, Bucher SJ, Brickner PW, Vincent RL, Lascher S. Latent tuberculosis and active tuberculosis disease rates among the homeless, New York, New York, USA, 1992-2006. Emerg Infect Dis. 2009;15(7):1109–11.
211. Szreter S. The importance of social intervention in Britain's mortality decline c. 1850? 1914: a re-interpretation of the role of public health. Soc Hist Med. 1988;1(1):1–38.
212. Pinet G. Good practice in legislation and regulations for TB control: an indicator of political will. Geneva: World Health Organization; 2001.
213. Atun R, Weil DE, Eang MT, Mwakyusa D. Health-system strengthening and tuberculosis control. Lancet. 2010;375(9732):2169–78.
214. World Health Organization. Green light committee initiative of the working group on MDR-TB of the Stop TB partnership: annual report 2008. Geneva: WHO; 2009.
215. Datiko DG, Lindtjorn B. Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. PLoS One. 2009;4(5), e5443.
216. Hafeez A, Mohamud BK, Shiekh MR, Shah SA, Jooma R. Lady health workers programme in Pakistan: challenges, achievements and the way forward. J Pak Med Assoc. 2011;61(3):210–5.
217. Dean HD, Fenton KA. Addressing social determinants of health in the prevention and control of HIV/AIDS, viral hepatitis, sexually transmitted infections, and tuberculosis. Public Health Rep. 2010;125 Suppl 4:1–5.
218. Fenton KA, Aquino GA, Dean HD. Program collaboration and service integration in the prevention and control of HIV infection, viral hepatitis, STDs, and tuberculosis in the U.S.: lessons learned from the field. Public Health Rep. 2014;129 Suppl 1:1–4.

219. Akachi Y, Zumla A, Atun R. Investing in improved performance of national tuberculosis programs reduces the tuberculosis burden: analysis of 22 high-burden countries, 2002-2009. J Infect Dis. 2012;205 Suppl 2:S284–92.
220. World Health Organization. Roadmap for childhood tuberculosis: towards zero deaths. Geneva: WHO; 2013.
221. How far have we come in reducing health disparities?: Progress since 2000: workshop summary. Washington, DC: The National Academies Press; 2012.
222. AHRQ. 2010 National healthcare quality and disparities reports. February 2011. http://www.ahrq.gov/research/findings/nhqrdr/nhqrdr10/qrdr10.html.
223. Carger E, Western D. A new way to talk about the social determinants of health. 2014. http://www.rwjf.org/en/research-publications/find-rwjf-research/2010/01/a-new-way-to-talk-about-the-social-determinants-of-health.html.
224. Healthy People 2020. http://www.healthypeople.gov/2020/about/DisparitiesAbout.aspx. Accessed 18 Feb 2014.

Chapter 12
Disparities in Lung Cancer Outcomes

Ching-Fei Chang, Gary S. Feigenbaum, and Michael K. Gould

Key Points

- Although overall lung cancer survival statistics are grim, certain subsets of patients appear to fare worse than others.
- Explaining this disparity in outcomes is difficult given the complicated interplay of multiple factors—social, environmental, cultural, and biological—which overlap and contribute to the problem.
- Barriers to timely and appropriate care—whether it be from socioeconomic reasons or various forms of discrimination—are perhaps the most important driving force for the increased mortality rates among these patients.
- In addition, given their high rates of smoking, as well as cultural misconceptions and mistrust of providers, improving education and communication is also key to increasing survival from lung cancer in these specific patient populations.

C.-F. Chang, M.D. (✉)
Division of Pulmonary, Critical Care, and Sleep Medicine, University of Southern California, Keck School of Medicine, 2020 Zonal Avenue, IRD 723, Los Angeles, CA 90033, USA
e-mail: cf3chang@yahoo.com

G.S. Feigenbaum, M.D.
Department of Internal Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

M.K. Gould, M.D., M.S.
Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_12

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States today, killing more men and women each year than breast, prostate, and colorectal cancers combined. This high death toll can be partially explained by the typically advanced stage of disease at the time of presentation, as well as a lack of effective treatment options. Even now, 5-year survival is only 16 % due to these unfortunate factors.

Prognosis remains poor despite numerous advances in the understanding and management of this disease. Major revisions to the TNM staging system and adenocarcinoma classification reflect a better understanding of the natural history of lung cancer in its many forms. Screening with low-dose computed tomography (CT) scans in high-risk patients can detect lung cancer at its earliest stages and boosts the chances of cure. New minimally invasive techniques (such as endobronchial ultrasound, electromagnetic navigation, and positron-emission tomography) have supplanted surgery in many settings and inspired alternate algorithms for the diagnosis and staging of pulmonary lesions. For patients with early stage disease, the development of robotic surgery and stereotactic body radiation therapy (SBRT) potentially offers more precise tumor elimination options with fewer complications, while for patients with advanced stage disease, the discovery of targeted molecular therapy for specific kinds of genetic mutations has revolutionized the therapeutic approach to lung adenocarcinomas (e.g., tyrosine kinase inhibitors (TKI) for EGFR and crizotinib for EML-Alk 4).

Although these are amazing innovations, they still may not have a significant impact on lung cancer death rates if their cost and availability limits access to only a very narrow subpopulation of Americans with lung cancer. Despite good intentions and the passage of major legislation, significant social, economic, and cultural barriers still persist that undermine access to appropriate health care for those at greatest risk for lung cancer. Thus, social revolution, rather than technological innovation, may be the true answer to improving lung cancer mortality in America on a large scale.

But dissecting out the root causes of disparities in lung cancer incidence and survival is extremely complicated. As John Muir once said, “When one tugs at a single thing in nature, he finds it attached to the rest of the world.” Sorting out discrete risk factors is nearly impossible because of how tightly they are intertwined and interdependent [1, 2]. This chapter seeks to define and understand how all of these variables intersect and impact each other (Figs. 12.1), resulting in worse lung cancer outcomes for specific subsets of the population.

Disparities Due to Socioeconomic Barriers

Socioeconomic factors such as income and level of education have been shown in numerous studies to be independent prognostic factors for undertreatment and poor survival in lung cancer [3, 4]. However, some experts believe that the contributions may not be equivalent—i.e., although education level may determine the onset of illness, income may be a stronger predictor of its outcome [5].

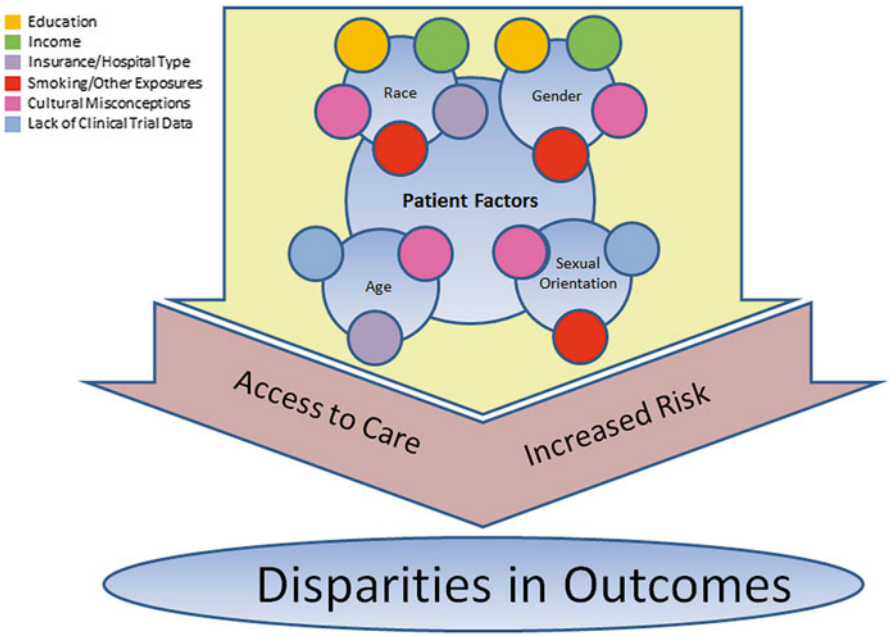

Fig. 12.1 The Intersectionality Theory: Disparities in lung cancer outcomes result from a complex interplay between genetic and social factors which leads to worse prognosis and reduced survival

Income

Patients from low-income families are clearly at higher risk for developing and dying from lung cancer. Studies have shown that patients from areas with the highest poverty levels (>15 %) are more likely to present with larger (>5 cm), poorly differentiated tumors with distant metastasis at diagnosis compared to patients from more affluent communities [6]. This disparity in outcomes can be explained by several factors.

Due to lack of resources, low-income patients tend to live in impoverished communities where there is a lack of access to: (1) grocery stores with fresh fruits and vegetable, (2) parks and other exercise facilities, (3) specialized cancer hospitals and physicians, and (4) adequate public transportation which can allow them to seek help elsewhere. On the flip side, these communities are often rich in primary and environmental tobacco exposure, illicit drug use, and crime [1, 7–9].

Because of the nature of their jobs, low-income workers tend to be exposed to more carcinogens—including second-hand smoke, asbestos, radon, and cooking or chemical fumes. They often have little flexibility in their work schedule or are afraid to ask for time off for medical appointments, especially when dealing with inherent

delays at public hospitals. The lack of a car may also discourage compliance with serial treatments and follow-up visits.

Clearly, low-income patients cannot afford good insurance coverage or out-of-pocket costs for cancer treatment, which are among the most expensive medical therapies available in the United States today. Thus, even when diagnosed at an early stage, these patients may still have poor outcomes if they cannot take action immediately. Their differing priorities and competing economic pressures may buffer their sense of denial and lead to further procrastination.

With the passage of the Affordable Care Act in 2012, this aspect may diminish as public health initiatives such as universal insurance coverage improve access to care. However, disparities in lung cancer outcomes may still exist if the working and living environments and high-risk behaviors of low-income patients do not change concurrently.

Education

No one can deny the fact that income and education are directly linked—higher education leads to higher paying job opportunities. But the extent of schooling can also impact lung cancer outcomes in an additional way as well.

Access to care depends on not only ability to pay, but also patient desires and motivation to seek the most aggressive and appropriate treatment possible. Studies have shown that the best lung cancer outcomes are usually seen at facilities which follow NCCN guidelines and evidence-based algorithms, often with the guidance of a multidisciplinary lung cancer team of experts. However, this is not universally available at all hospitals and most often occurs at an academic center, comprehensive cancer institute, or integrated systems such as Kaiser Permanente or the Veterans Health Administration. Ironically, some studies show that private community hospitals have the most inconsistent, non-guideline-based care [10].

The level of education can directly impact which type of hospital the patient selects. Poorly educated patients may seek care at public teaching hospitals, where resources are often limited and care may be delayed. Patients with higher education tend to research their disease state online and seek care at the best hospitals possible, even if it is quite a distance away. They understand the need to be aggressive and are willing (and able) to sacrifice time and money to pursue the most effective treatment modalities at centers with the most experience. Their education also makes them more proactive and knowledgeable about the value of screening and early diagnosis. In addition, highly educated patients tend not to smoke, although several studies have shown that the effects of childhood smoke exposure do not dissipate and contribute to increased risk for lung cancer later in life.

The current push for more widespread public education about the dangers of smoking, lung cancer screening, and available treatment options does not address the most basic deficit of all—which is improving access to education in general. If an adequate educational foundation can impact lung cancer outcomes, then societal

changes through legislation may actually alter the course of this disease more quickly and effectively than any major breakthrough in advanced cancer technology.

Disparities Due to Race

Race is a commonly identified risk factor for poorer outcomes in lung cancer [11]. On the surface, it may imply genetic differences between ethnic groups such as African Americans, Asians, and non-Hispanic Caucasians—e.g., African Americans appear to be genetically more vulnerable to the damaging effects of cigarette smoke [12] while East Asians often carry targetable EGFR mutations [1]. Or it may suggest cultural differences in the processing of information, mistrust, or acceptance of western treatment methods [1, 13–15]. Or it could refer to actual provider discrimination in the diagnosis and management of lung cancer. But in reality, race also implies socioeconomic and educational disparities, which clearly can impact access to timely and appropriate care.

Despite the election of an African American president and major landmark legislation over the past century to reduce social inequalities, racial discrimination still exists in the United States. There is no other way to explain why the poorest zip codes in the nation, defined by a poverty rate of >20 %, are communities comprised predominantly of ethnic minorities, usually black or Hispanic [9]. For example, racial analysis of the 11 Surveillance, Epidemiology, and End Results Program (SEER) areas demonstrated that African Americans, Hispanics/Latinos, and American Indians/Alaskan Natives live in the most impoverished areas [9]. In another study, black patients were 26 % more likely than whites to reside in poor communities, and much like the subgroup of low-income patients, they present with larger tumors which are often undifferentiated and have distant metastasis at diagnosis [6].

Indeed, many experts feel that when socioeconomic variables are adjusted for, no differences in lung cancer mortality can be seen as a result of race. In an analysis of almost 11,000 SEER Medicare patients, Bach et al. found that the most important factor impacting survival among different races was the receipt of surgical resection; compared to their white cohorts, blacks were 12.7 % ($p<0.001$) less likely to receive this appropriate intervention [11]. Similarly, in as study of over 900 patients at the Reed Army Medical Center, Mulligan et al. found that if universal access to appropriate medical care was available, no racial disparities in lung cancer mortality could be observed [16]. Multiple other authors concur with this finding of socioeconomic factors driving the differences in racial lung cancer outcomes [6, 16–20]. Berger et al. embodies this popular opinion by stating that the "link in support of a biologic or genetic difference among different racial or ethnic groups to explain the disparity in outcomes is still weak" [21].

There are a few papers which disagree with this consensus. Farjah et al. proposed that studies to date on this issue have not measured important differences in FEV1, comorbidities, or performance status between races which may also account for

discrepancies in outcomes [17]. Williams et al. feels that, even when patients of color have the same education and income level, as well as the same histology and stage of lung cancer, the outcomes may still be worse than those for their Caucasian counterparts. For example, although they may have equivalent mortality rates at the lowest socioeconomic levels, black men are more likely to die from lung cancer than white men within the highest educational brackets. Similarly, when their level of schooling is low to midlevel, black women have a lesser or equivalent risk of death than their white counterparts; however, when they are highly educated, black women are more likely to die from lung cancer than white women. Thus, although more schooling improves overall outcomes within a racial group, it paradoxically unmasks and underscores survival differences between racial groups, despite perceived educational and economic equivalence [1].

In addition, the damaging effects of cigarette smoking seem to be racially and genetically based. Evidence suggests that not only are African Americans more vulnerable to the toxic effects of tobacco use [12], but nicotine sensitivity is higher and clearance is lower, thus contributing to low sustained quit rates, despite the fact that they tend to start smoking later in life and smoke fewer cigarettes overall [22, 23]. However, subgroup analysis demonstrates that, at every socioeconomic level, black women smoke less frequently than white women, perhaps due to a higher level of religious involvement. This may also explain the same trend in adolescent African Americans [24, 25]. Certain ethnic immigrants are also less likely to smoke than their American-born counterparts [26] and have a correspondingly lower lung cancer mortality rate [27]; unfortunately, both of these rates rise with increased length of stay in the United States [28]. Based on the SEER database, the highest prevalence of smoking was found in American Indian/Alaskan Native women (38.6 %) and men (27.4 %), and the lowest prevalence in smoking was found in Asian and Hispanic/Latino women (7.9 %) [9].

Of note, while the association between race/ethnicity and worse lung cancer outcomes has been observed for African Americans, American Indians, Alaskan Natives, Hispanic/Latinos, and Pacific Islanders, it appears that East Asian minorities may have a better prognosis overall due to a higher prevalence of more treatable, non-smoke-related cancers such as adenocarcinomas with EGFR mutations [1].

Whereas the debate continues in regards to whether racial disparities in lung cancer are due to genetic/biologic differences or due to socioeconomic factors, the impact of cultural perceptions on the delivery of care is well accepted. Wisnivesky's group published a recent paper which found that almost 33 % of the worse outcomes among black versus white patients can be explained by their fatalism, mistrust of providers of a different racial group, and negative beliefs regarding surgery [29]. Thus, whereas socioeconomic factors may impact the incidence and timing of lung cancer diagnosis, cultural attitudes and beliefs play an important role in what unfolds afterward [14, 15].

This influence of culture on the acceptance of recommended care has been studied most extensively in African Americans. Despite having early stage resectable

lung cancer and adequate pulmonary reserve, statistics show that blacks are significantly less likely to receive surgery than whites (64 % vs. 76.7 %), resulting in a much lower 5-year survival [11]. However, the striking discrepancy in operative rates is not exclusively due to socioeconomic barriers [30].

If cost and access to treatment are not issues, then an alternative explanation for continued discrepancies in care may be subconscious provider discrimination. Clearly, inherent physician biases, whether intentional or not, may lead to misconceptions regarding the patient's willingness or likelihood of adherence with treatment and personal preferences [9]. Providers may frame the information regarding diagnosis and management options in such a way that the patient's decision-making is skewed toward a less optimal plan [9].

However, patients may also negatively affect their own outcomes based on their cultural perceptions, regardless of how objective and well meaning the provider is. For example, McCann et al. showed 18 % of black patients refuse surgery for lung cancer compared to only 5 % of white patients [31]. Several reasons have been hypothesized as to why racial/ethnic minorities may refuse appropriate surgery for early stage disease. These include:

1. Distrust of the medical system and their provider
2. False beliefs about their diagnosis and prognosis
3. Reliance on faith and prayer to cure them
4. Skepticism about cancer treatment
5. Belief that exposure to air during surgery will spread the cancer (a misguided notion that was promoted by the American Medical Association)
6. Belief that acceptance and discussion about their diagnosis will ensure death—fatalism [9, 13, 14, 17, 32]

Depending on their education level and degree of integration into mainstream society, racial/ethnic minorities may find it difficult to navigate a complex bureaucratic medical system or may have inherent distrust of providers who are of a different race [33]. For example, a study showed that more blacks refused appropriate surgery when the diagnosis and treatment options were presented to them by a virtual physician of a different race, even if there were no perceivable differences in sense of trust, level of engagement, and communication styles [34]. In addition, based on their cultural biases, patients may be afraid of surgery compared to less invasive (but inferior) modalities or hesitate to ask for pain medications and hospice referrals when appropriate [35].

Thus, race, culture, genetics, and socioeconomic circumstances all appear to influence lung cancer outcomes simultaneously [2, 9]. As one of the best examples of the intersectionality theory, these four factors are so tightly intertwined and interdependent that race alone cannot be dissected out as an independent cause of worsened lung cancer survival.

Disparities Due to Healthcare Access

Walter Cronkite once said that "America's health care system is neither healthy, caring, nor a system." According to the U.S. Census Bureau in 2009, 48.6 million people in the United States lacked health insurance [36]. This translates into approximately 45,000 excess preventable deaths per year, or equivalently, a person dying every 12 min [37]. Yet even when patients are insured, access to medical care does not always translate into better outcomes. Depending on type of insurance, hospital resources, and whether treatment decisions are guideline driven or seeped in individual preferences, the care given may not be high quality or appropriate.

Insurance Type

Clearly, the absence of health insurance can directly block access to nonemergency care. However, even with insurance, disparities in lung cancer outcomes can still exist based on the type of coverage.

Previously, Slatore et al. published an exhaustive systematic review of available literature on the association between type of insurance and survival from lung cancer. As expected, they found that patients with no insurance or only Medicaid consistently had worse outcomes than patients with Medicare or private insurance. This disparity may be rooted in the fact that indigent and underserved patients are more likely to smoke and avoid routine health maintenance, thus presenting to medical attention at a very late stage of lung cancer. But this disparity may also result from lack of access or undertreatment of these patients due to their insurance status [38].

Bradley and colleagues published a series of four papers that evaluated the impact of having Medicaid on various subpopulations of lung cancer patients. At all stages of lung cancer, regardless of age or gender, it appears that all-cause and cancer specific mortality rates were much higher in comparison to patients with Medicare or private insurance [39–43]. Interestingly, other studies have found that patients with combined Medicare/Medicaid did worse compared to patients with Medicare alone [44], and even patients who underwent curative-intent surgical resection had a discrepancy in outcomes related to Medicaid status [45].

Medicaid is not unique in being associated with poor outcomes. Compared with either health maintenance organization (HMO) or fee for service (FFS) coverage alone, the combination of HMO and FFS has been associated with increased all-cause mortality (but not lung cancer-specific) for unclear reasons [46]. This is interesting because patients with the latter combination were more likely to receive surgery compared to patients with only FFS plans [46]. Furthermore, other studies showed that private/commercial insurance was associated with higher surgery rates compared with non-commercial insurance [47, 48].

Although there is no arguing that uninsured and Medicaid patients have the worst outcomes in lung cancer [29, 38], there is conflicting data in regards to which kind

of other insurance is superior—Medicare or private/commercial. Based on a study by Potosky et al., it appears that private insurance status was associated with lower rates of guideline concordant care, and that ironically, patients with public insurance, or a mixture of public and private plans, were more likely to receive stage-appropriate care [10]. In contrast, Harlan and colleagues found that adherence to NCCN guidelines was highest among those with private insurance and lowest among those with non-private insurance, with uninsured patients falling somewhere in between [49]. Groth et al. also found that patients with private insurance were more likely to undergo lobectomy for early stage lung cancer than patients with Medicare, Medicaid, or no insurance at all [50].

Finally, even within a single academic medical center, where 29 % of patients were covered by an indigent care plan (defined as Medicare or a "county" health plan), discrepancies in outcomes were found based on insurance type. As Yorio et al. discovered, the odds of receiving "standard therapy" were dramatically reduced for patients who were covered by an indigent plan compared to private insurance. Among these socioeconomically disadvantaged patients with early stage non-small cell lung cancer (NSCLC), the hazard of death was almost twice as high and they were less likely to undergo surgery compared to privately insured patients (OR 0.13, 95 % CI 0.04–0.43). At first, the authors considered patient factors as an explanation for these findings; their indigent patients tended to be nonwhite male smokers and usually presented at a more advanced stage of disease with non-adenocarcinoma histology. They also often had smoking-related comorbidities which affected their surgical candidacy. However, even after controlling for all of these variables, socioeconomic status (and resultant insurance type) remained an independent risk factor for undertreatment and poor survival. Interestingly, although ethnic minority status also had a trend toward treatment disparities, it was not statistically significant [51].

Hospital Type

Another factor accounting for disparities in lung cancer outcomes is hospital type. Even if patients have insurance and access to care, the characteristics of the treating institution can influence the likelihood of survival. Since surgery offers the best chance at cure for early stage disease, the frequency at which lung resection occurs at a particular hospital can help explain discrepancies in mortality rates [52].

Hospitals that traditionally have lower surgical volumes and no dedicated thoracic surgeon tend to offer lung cancer resection less frequently due to their lack of experience and expertise [52–55]. Thus, it is no surprise that seeking care at smaller hospitals may lead to a poorer prognosis.

It is also not surprising that large safety net and public hospitals tend to offer surgery less often to lung cancer patients due to a lack of resources and the fact that many of their underserved patients present with advanced stage disease [39, 52]. These patients are usually indigent or undocumented, and thus have Medicaid or no

insurance at all. As a result, their insurance type can drive hospital selection, which then, in turn, impacts surgical decision-making, thus leading to further disparities in lung cancer outcomes. The exception to the rule, however, is county teaching institutions, where the chances of getting surgery are much higher [52].

What is interesting, however, is that the racial composition of the hospital patients also plays a role. Lathan et al. compared hospitals with a higher percentage of Medicare-insured black patients with those who served primarily white patients; they found that if the racial composition was ≥30 % African American, surgery was less likely to occur for early stage disease. This was in addition to, rather than because of, racial disparities. All patients in those hospitals, regardless of race, received less surgery [52].

Therefore, hospital type is a key determinant of survival rates for lung cancer. The Affordable Care Act, which theoretically will improve access to care by providing universal insurance coverage, may not solve this disparity if the quality of care at all hospitals is not standardized. Ideally, hospitals should follow national guidelines in lung cancer treatment and refer their patients to the closest major cancer center if they are unable to provide guideline-based care because of lack of experience or resource limitations.

Gender Disparities in Lung Cancer

The popular paradigm put forth in the best-selling book, "Men are From Mars, Women are From Venus" may hold true in more than just the psychology of relationships. From the perspective of lung cancer outcomes, the disparities between men and women are so striking that many experts believe they may actually represent different disease states [56–58] that require alternate approaches to treatment. In the era of personalized molecular medicine, where one glove no longer fits all, this not only translates into the need for individually tailored therapies, but we also need to rethink the design and interpretation of clinical trials with such differences in mind [56, 57, 59–61].

In light of this new appreciation of biological differences, it is ironic that the epidemic of lung cancer among women may have resulted in part from a desire to be more like men. Since the nineteenth century, women have faced inequality in several arenas, and in their quest to break free from traditional stereotyped roles, more and more women adopted what had been a predominantly male habit—smoking. Since the 1940s, tobacco companies aggressively portrayed smoking as a sign of independence among women, and after a latency period of several decades, we are now seeing the unfortunate consequences in recent years [60]. Although smoking cessation campaigns have been successful in reducing overall female tobacco use since the 1960s [57, 61], the habit continues to increase in prevalence among adolescent girls. That this demographic group is at risk should not be surprising given the fact that men and women may smoke for different reasons, with the latter

more frequently using cigarettes to boost their self-image; thus, teenage girls with depression and weight issues are particularly vulnerable [57, 59, 60, 62, 63].

As a result, some experts estimate that the incidence of female lung cancer in the U.S. has jumped by 600 % in the past 50 years [57]. Since 1987, lung cancer has exceeded breast cancer as the number one cause of death among women [64]. Annually, 30,000 more women die of lung cancer than breast cancer, and the gap continues to widen [58]. Part of this discrepancy may be due to effective public education, vigilant screening, and improved treatments for breast cancer. However, a more concerning possibility is the fact that the biology of lung cancer in women is different from that in men, and up until now, we have been treating them the same.

Multiple studies have shown that female lungs are more vulnerable to the effects of carcinogens [58, 63–65]. This may be partially attributed to the fact that they have reduced pulmonary reserve. Although the lungs appear to develop at a similar pace for both genders throughout childhood, at puberty boys have a major growth spurt which results in larger airway calibers with less bronchoreactivity [58]. Given the same age and dose of tobacco exposure, women suffer more damage and decline in FEV1, with a resultant higher susceptibility to COPD and lung cancer compared to men [58, 62]. In fact, females are at a 1.5–2.7-fold increased risk of developing lung cancer compared to males [65, 66].

Early second-hand smoke (SHS) exposure also seems to plays a role. Compared to children raised in a nonsmoking household, those who grew up surrounded by SHS have 30 % increased odds of developing lung cancer as an adult if exposed during the first 25 years of life, yet their risk of lung cancer is reduced dramatically if exposed after the age of 25 years [67]. Yet upon stratification by gender, there is a disparity in this window of vulnerability. Whereas the damaging effects of SHS appear to plateau at age 20 for males, this risk threshold extends up to age 25 for females [58, 63]. Thus, females are more prone to developing lung cancer than men, despite similar or lesser exposures.

Despite the surge of tobacco use in the past half century, a significant fraction of women who develop lung cancer are never smokers [57, 61, 62, 64]. In the United States, approximately 15–20 % of lung cancers occur in nonsmokers, and of these, 70–80 % are women [62]. This phenomenon of lung cancer in female nonsmokers may be partially explained by unintentional exposure to environmental carcinogens, such as indoor fumes from cooking, residential radon, and second-hand tobacco exposure, which can increase the risk of lung cancer by 24–30 % [56, 63, 66].

Of historical interest, the segregation of women to the home and men to the workplace in past decades resulted in distinctly different patterns of exposures accounting for lung cancer in nonsmokers. Among nonsmoking men who developed lung cancer, the chief carcinogens they were exposed to were found in the workplace: asbestos, radon, and chemical toxins. The majority of nonsmoking women, however, developed lung cancer as a result of second-hand smoke from their husbands [68]. These patterns of predominant carcinogen exposure are changing as a result of changing roles of men and women in the workplace and home. As smoking cessation efforts continue and laws are passed banning cigarettes in work and public places, the impact of tobacco on the development of lung cancer may

diminish, and other exposures and factors (such as genetics) will become more important contributors to lung cancer.

Despite a higher incidence and greater vulnerability to lung cancer, women have one major advantage over men: the type of lung cancers they develop tends to be less advanced and more responsive to treatment. Multiple studies have shown that regardless of the histology and stage, women appear to have "superior survival" statistics compared with men [58, 59, 61, 62, 64, 69, 70].

Compared with men, lung cancer in women tends to develop at a younger age, is detected at an earlier stage, and is predominantly adenocarcinoma that is frequently associated with EGFR mutations [56, 58, 61, 62, 71]. On average, these features result in better survival and fewer treatment side effects, if not absolute cure. In the presence of EGFR mutations, treatment with TKI have shown a response rate of up to 75 % in advanced NSCLC [72]. Even when their tumors lack actionable mutations, however, women tend to have better responses than men to standard platinum-based chemotherapy regimens [60]. And if they are fortunate enough to be diagnosed with early stage disease, women historically have had lower operative mortality rates than their male counterparts [57, 63].

In contrast, lung cancer presents very differently in men. Although adenocarcinoma is still the most prevalent subtype, smoking-related forms such as squamous cell and small cell are seen more frequently than in women [62]. Men with lung cancer tend to be diagnosed at a more advanced stage and frequently have tumors that lack EGFR mutations and are less responsive to surgery or chemotherapy. Thus, while women are at higher risk of lung cancer, they tend to develop forms which are milder and easier to treat, with better overall prognosis than men [70].

These distinctions in lung cancer presentation and outcomes by sex support the idea that biological and behavioral differences between men and women may influence lung cancer disparities. For example, cervical infection with HPV can lead to airway infection by HPV—either due to hematologic dissemination or risky sexual practices—which can then result in viral-induced squamous cell airway tumors, particularly in Asian women [56, 64, 69, 73]. Another example is HER2/neu or BRCA mutations, which are commonly associated with breast cancer, and are now being found in lung cancer tissue as well. Although studies have not shown benefit in giving lung cancer patients trastuzumab (a monoclonal antibody to HER2/neu) in addition to standard chemotherapy [74], this remains a potential target for therapy in the future. BRCA1 overexpression appears to increase the sensitivity of tumors to taxol therapy and therefore may help tailor treatment [64].

A high estrogen milieu (due to endogenous estrogen production or use of hormone replacement therapy (HRT) after menopause) is also being implicated in the pathogenesis of lung cancer and is a potential therapeutic target. No longer considered just a "sex steroid" involved in breast, ovarian, and endometrial cancers, estrogen is now being investigated as a controller molecule for abnormal proliferation in the lungs, acting as a direct carcinogen in forming DNA adducts [60, 62]. In vitro studies have shown a 17-fold increase in proliferation of lung cancer cell lines when incubated with B-estradiol. Early menopause, which ironically increases the risk of

cardiovascular disease in women, seems to decrease the risk of lung adenocarcinoma in women [57, 69].

The role of hormone replacement therapy (HRT) in the pathogenesis of lung cancer is controversial. Initially, the Women's Health Initiative study suggested a higher rate of lung cancer in female smokers on HRT. However, a post-hoc analysis found that this was only true when patients were supplemented with both estrogen and progesterone, not estrogen alone. Paradoxically, other studies have found a protective effect of HRT against the development of lung cancer in current smokers, so the jury is still out in regards to whether estrogen exerts a positive or negative impact on lung cancer [58, 61, 69, 75, 76].

Estrogen receptors (ER) may provide another therapeutic target in the battle against lung cancer in women. Alpha and beta ER are normally found in pulmonary tissue; the presence of ER-beta, however, has been demonstrated in 45–70 % of resected NSCLC tumors in both genders [56, 62, 77]. Soy is known to competitively bind to ER, and therefore high soy intake may exert a protective effect against lung cancer [69]. Studies have also shown decreased lung cancer mortality (although no reduction in incidence) in women who are on tamoxifen for a history of breast cancer [78]. Genetically, ER-beta seems to track with EGFR mutations in many patients and may provide another surrogate marker for selection of TKI candidates [79]. In fact, concurrent administration of fulvestrant (ER blocker) with gefitinib has been shown to sensitize the tumor to TKI and thus may synergistically increase response rates [80, 81].

A final potential therapeutic target may be aromatase. This enzyme catalyzes the conversion of androgens into estradiol and is especially important in post-menopausal women. Even when the estrogen milieu is low, lung cancer can produce its own local estrogen via high levels of aromatase, and this has been found to be a poor prognostic marker [60, 62, 77]. Aromatase inhibitors may therefore be useful in reducing triggers for proliferation [77].

In addition to the obvious hormonal differences between men and women, women may carry other types of genetic alterations which may explain both their increased vulnerability to the development of lung cancer and their superior survival compared with men. Because of the presence of polymorphisms in CYP detoxification enzymes, women tend to express more DNA adducts compared to men, have a higher level of CYP1A1 which activates certain carcinogenic polycyclic aromatic hydrocarbons (PAH), and have a reduced level of GSTM1 which prevents the clearance of toxic metabolites [57, 58, 60, 62, 69]. This accumulation of reactive intermediates in women may not only increase the risk of lung cancer [60, 64] but may also help explain the higher incidence of COPD and FEV1 decline in women with minimal tobacco exposure, both of which are also independent risk factors for the development of lung cancer [58].

Female patients have also been found to have a lower DNA repair capacity (DRC), which is necessary for fixing nucleotide mismatch or mutations [57, 58, 60, 62]. This may paradoxically increase the risk of lung cancer and yet simultaneously improve the response to platinum-based chemotherapy. Platinum-based agents work by forming DNA adducts which halt the cell cycle. An inability to repair these

DNA adducts encourages apoptosis within cancerous cells [60]. Studies have shown improved survival in Stage 4 NSCLC when patients who have lower DRC are given standard chemotherapy [82].

Not all genetic defects in women confer an unfavorable outcome, however. EGFR mutations are the main driving mutations behind 8–10 % of NSCLC, especially adenocarcinomas, and are typically found in women, nonsmokers, and Asians. Three major studies have documented a statistically higher rate of EGFR mutations in women compared to men—ranging from 19 to 38 % in females compared to 9–14 % in males [64]. This lends women a distinct survival advantage because of the exquisite sensitivity of these tumors to TKIs, which have demonstrated superior outcomes in clinical trials relative to traditional chemotherapy [83, 84]. In addition, EGFR mutations are often found in adenocarcinoma in situ (AIS, formerly known as BAC), which due to its indolent growth pattern already has a better prognosis than other forms of lung cancer. In addition to their predilection for EGFR mutations, women are also two- to fourfold more likely than men to have AIS [56, 62, 69].

Of note, women have also been found to carry Kras mutations more frequently than men (26.2 % vs. 17.4 %) [85]. Kras mutations are present in approximately 10–30 % of adenocarcinomas, tend to be mutually exclusive to EGFR mutations, and unfortunately have no specific targeted therapy [62]. Indeed, studies have found increased mortality when patients with Kras mutations are given TKIs [72]. Women with Kras mutations have a worse prognosis.

Finally, the discussion of gender and lung cancer outcomes would not be complete without addressing lung cancer in gay, lesbian, or bisexual patients [86]. This highly marginalized group may be the most neglected of all minorities because most surveillance and research databases have no options for alternate sexual preferences, including the U.S. Census and SEER [86, 87], and therefore, there is less data on disparities. As a result, health disparities for this minority group have received little attention until recently.

Currently, the few epidemiologic studies that exist suggest that up to 6 % of all patients seen by physicians in the United States self-identify as members of a sexual minority group. However, many physicians are untrained and report feeling uncomfortable in addressing special issues related to treating this patient population. Studies show that almost 40 % of clinicians are “sometimes or often” uncomfortable providing medical care to gay patients, and 67 % of health providers report seeing “substandard care” being given to members of sexual minority groups [88]. Indeed, it is estimated that only 3 h and 26 min are devoted to the teaching about special health issues related to homosexuality in 4 years of medical school [89]. But compared to the general public, members of this minority group exhibit a much higher rate of smoking, alcoholism, and drug use, and thus patients from sexual minority groups represent an under-appreciated, under-treated, high-risk demographic for lung cancer and other diseases [86–88, 90, 91].

Interestingly, despite an equal understanding of the dangers of smoking and support of banning smoking in public places [87], members of sexual minority groups smoke heavier and longer than their heterosexual counterparts—approximately twice the volume, starting earlier in their youths, and with much lower quit rates

[86, 87, 90]. Smoking rates among gays, lesbians, and bisexuals ranges from 38– 59 % in youths and up to 50 % in adults, compared to an average of 28–35 % and 28 % in heterosexual adolescents and adults, respectively [90].

Given these facts, it should be no surprise that the incidence and mortality of lung cancer is much higher among gay men and bisexual patients, with the same pattern of racial disparities (blacks with worse outcomes than whites) as that seen in the general population [86]. In contrast, the impact of smoking may be less pronounced in lesbian women than their heterosexual counterparts. Despite greater tobacco exposure, lesbian women appear to have statistically better lung cancer survival. The only explanation proposed for this perceived resilience against the damaging effects of tobacco thus far is lagtime bias; some experts feel that lesbian women, as a group, only started to smoke heavily recently. Thus, their lung cancer incidence may increase over time and actually peak a few decades from now. Based on these findings, it seems the disparities in lung cancer outcomes among sexual minorities may be a predominantly sociobehavioral phenomenon related to heavy smoking and lack of healthcare maintenance, rather than based on biologic and genetic differences.

The most promising solution to reducing lung cancer-related disparities in sexual minorities may involve improving existing communication and support. Part of the reason why sexual minorities are medically underserved is because they tend to avoid routine healthcare visits (including preventive services) because of fear of "insensitive" providers and perceived poor communication [88]. In addition, smoking cessation programs need to be geared toward their special needs, as their triggers for smoking relapse are usually different and specifically revolve around anxiety, depression, and the stress of living in an often homophobic society [87].

Given the complicated milieu of genetic, hormonal, behavioral, and environmental factors that may be differentially involved in the development of lung cancer among persons of different genders, future treatments must be highly personalized with the consideration of gender-specific needs to avoid disparities in care. This includes not only strategic use of targeted therapies against a variety of hormonal receptors and genetic mutations that are distributed differently among men and women, but also more preventive education and aggressive smoking cessation campaigns directed specifically at adolescent females, gays, lesbians, and bisexuals.

Disparities Due to Age and Comorbidities

Age

Ralph Emerson once said that "All diseases run into one—old age," implying that age is an umbrella term for the comorbid diseases which naturally accumulate as the body grows older. However, the definition of what is considered "old" is controversial and subject to interpretation. Historically, 65 years have been used as a threshold, but as projected lifespan steadily increases due to healthier lifestyles, modern

medicine, and preventive measures, this demarcation of what is considered "old age" becomes dynamic and blurred [92].

Why does it matter? In regards to therapeutic decision-making, age alone theoretically should not matter. As Mark Twain once said, "Age is an issue of mind over matter; if you don't mind, it doesn't matter."

However, despite this enlightened adage, age has always been used in the past as a criterion for exclusion in the field of medicine—not only for determination of surgical candidacy, but also for enrollment in clinical trials. Ironically, the elderly have been highly underrepresented in studies that were designed to cure or palliate diseases they are more prone to develop, especially with regards to lung cancer [92–102].

Unless we change our attitude toward age, this dilemma of inappropriate extrapolation of results from younger patients onto older patients will only increase in the future [93, 94]. Some experts estimate that, due to lengthening lifespan and reduced births, 1:5 people will be over the age of 65 by year 2020, and the number of patients >85 years will be quadrupled by year 2030 [92].

Our thinking about age must shift to prepare us for the increasing number of older adults who will be seeking medical care in the near future. Unlike young patients who are more homogenously resilient, elderly patients are a mixed lot—some are quite fit, while others are quite frail [94, 103]. Physicians need to recognize that a patient's "calendar age" may not match their "biologic age" and make individualized treatment decisions based on the latter rather than the former [92, 103].

Keeping this in mind, it should also be appreciated that other than smoking, the most important risk factor for developing lung cancer is older age [92]. In the U.S., over two-thirds of all lung cancer patients who die are 65 years or older, with 70 being the mean age at diagnosis based on SEER data [92, 93]. Unfortunately, older age is sometimes used as an excuse not to treat. Even in the absence of comorbidities, it is mistakenly presumed that due to reduced renal, hepatic, hematologic, and cardiopulmonary reserves, elderly patients will not be able to tolerate any of the demands of surgery, chemotherapy, and radiation [92, 93]. As a result, these patients are often undertreated [92–94]. Age alone has caused physicians to inadvertently withhold guideline appropriate care from almost 50 % of the population in need [93].

It is true that aging is associated with reductions in drug clearance and bone marrow reserves [92, 93], but to what extent these toxicities are tolerable is unclear. Because most clinical trials have excluded patients older than 70, the safety and efficacy of standard lung cancer therapy in this special population is relatively unknown [94, 97–102].

Among those with early stage disease, elderly patients were only a third as likely to undergo resection as their younger counterparts, and the likelihood decreased by 65 % for each decade of life after age 65 [104]. Bias against surgery in this population maybe due to a fixation on chronological age rather than appropriate evaluation of performance status and comorbidities [94, 105, 106]. Physicians and family may believe that the life expectancy of an octogenarian is already limited and that the patient may die of other conditions before they die of their lung cancer. However, the U.S. Census reveals that an 80-year-old citizen can expect to live an average of 7–9 more years, which exceeds the life expectancy of untreated lung cancer [104].

Because of increasing evidence demonstrating that surgical resection can be safely accomplished in the elderly with few comorbidities, the British Thoracic Society Guidelines state that the decision to withhold radical surgery in cases of early stage lung cancer should not be based on age alone [107]. Indeed, elderly patients have a similar disease-specific survival and recurrence rate once other causes of death are excluded; it is important to differentiate that the higher all-cause mortality rates in older adults are due to the presence of comorbid diseases rather than to age itself [92, 108–111]. Although a pneumonectomy does appear to carry an increased risk of death in these older adults [94, 112, 113], lobectomies and sleeve resections can provide similar benefit with less post-operative morbidity and post-operative declines in quality of life [92, 114, 115]. With advances in laproscopic and robotic techniques, future studies will likely further confirm that age itself is not a contraindication to surgical intervention, even in octogenarians [94, 116].

Similarly, the data is sparse regarding the impact of age on chemotherapy or radiation outcomes [93, 94]. It is possible that the risks may be over-exaggerated and that with strategic planning and an acceptance of a slightly increased toxicity profile, elderly patients can also benefit from aggressive care. Interestingly, in the few elderly-specific clinical drug trials that exist, there is actually a lower adverse event rate compared to age-unspecified trials [93]. This may be due to more careful treatment plan designs which avoid certain age-related vulnerabilities, such as bypassing cisplatin in those with reduced bone marrow and renal reserve [92, 93], lowering dosages or total number of chemotherapy sessions [93, 111, 117], and/or providing hematopoietic support as needed [93]. Although older trials found that using single-agent chemotherapy was safer than the standard platinum-taxol doublets, newer studies are now suggesting better survival with the latter option, albeit with higher toxicity profiles, especially hematologic complications [92, 93, 95, 118, 119]. For elderly patients with advanced lung cancer and actionable mutations, targeted molecular therapy holds promise as a safe and efficacious treatment option with a much milder adverse effect profile [120, 121].

In patients presenting with Stage III and IV disease, advances in radiation therapy like stereotactic body radiation therapy SBRT have made treatment safer and more precise [122], preserving further reductions in cardiopulmonary function by avoiding unnecessary bystander damage to surrounding tissues. When combined with definitive chemotherapy, it appears that serial, rather than concurrent treatment in the elderly may be safer without significant loss of efficacy [93]. Even in early stage disease, SBRT may be useful in frail or older patients—with some studies showing equivalent results to surgery, mostly due to the low risk of recurrence in their remaining natural life spans.

Comorbidities

Because age not only increases the risk of lung cancer, but the frequency of comorbidities as well, physicians are often afraid to treat lung cancer aggressively due to the risk of potential iatrogenic complications [96].

As a result, 24–70 % of all cancer patients with comorbidities are not treated according to guidelines [96]. Indeed, studies have shown that 68 % of untreated patients had "comorbidities" written in their chart as the reason for no intervention [96, 123], which, in retrospect, may explain their worse outcome.

But how real is this increased risk of treatment-related death and disability among patients with comorbid chronic diseases? Since patients with severe comorbidities are often underrepresented in most clinical trials [96], the assumption may be largely theoretical.

More importantly, when statistics show that cancer patients with comorbidities have overall poorer survival, is this because of the underlying conditions, or the undertreatment of the cancer? In other words, is this a disparity that is potentially modifiable?

In lung cancer, the prevalence of serious comorbidities is 26–81 %, not only because of the advanced age of the population, but because smoking also increases the risk of COPD, CAD, hypertension, and stroke [96, 124]. In fact, lung cancer patients tend to have COPD and CAD at twice the frequency of the general population [124]. The 5-year mortality for lung cancer patients with comorbidities is 1.1–1.5 times higher than those without, which may be less dramatic than effects of comorbidities observed in breast or colon cancer due to the fact that the baseline mortality rate is already high [96].

Even after adjusting for age, cancer stage, and treatment, evidence still exists for worse outcomes among lung cancer patients with comorbidities. Unlike patients with breast or colon cancer, this population appears to have an elevated cancer-specific mortality risk rather than an all-cause mortality risk [96]. This disparity may result in part from the fact that these patients are routinely undertreated—whether it be from physician reluctance to start, or patient inability to complete therapy [96, 125].

For example, many studies have shown that patients with comorbidities are less likely to be offered chemotherapy, and if they do receive chemotherapy, they are more likely to get a reduced dose or may not complete all of the treatments due to side-effects or adherence issues [96]. However, treatment-related complications such as thrombocytopenia, febrile neutropenia, and death from neutropenic infections are more commonly seen in patients with other underlying diseases, so the benefits must always be weighed carefully against the risks [96, 125, 126].

In addition, it is well-accepted that patients with comorbidities have an increased risk of post-operative complications [127]. However, this fact may not be enough to justify the 25–58 % lower odds of receiving appropriate lung cancer surgery [96]. For example, patients with severe COPD may actually have minimal or no loss of lung function with upper lobectomies, which may also provide the benefits of lung volume reduction. Compared with the certainty of death from untreated lung cancer, even a four- or five-fold increase over the baseline 2–4 % risk of fatal perioperative complications does not seem so excessive as to prohibit a conversation with the patient about surgical options.

Finally, it is interesting to note that, although significant comorbidities may deter aggressive treatment once lung cancer is diagnosed, certain types (such as coronary

artery disease, diabetes, or arthritis) may actually improve screening and thereby improve outcomes. Studies have shown that if the chronic disease is unstable or related to depression, alcoholism, or dementia, it may detract attention away from the signs and symptoms of cancer and thus delay diagnosis [96]. However, other well-compensated types may prompt more frequent clinic visits, utilization of screening, and detection of early stage disease [96]. Thus, the presence of comorbidities does not automatically result in lower lung cancer survival.

HIV

Human Immunodeficiency Virus (HIV) patients present an interesting subgroup with comorbidities. While the widespread use of highly-active antiretroviral therapy (HAART) has transformed HIV from a terminal diagnosis into a chronic disease state [128–131], many practitioners are still under the misimpression that complications from AIDS will kill a patient before lung cancer does. Even if the infection is under excellent control with undetectable viral loads, many oncologists are hesitant to administer chemotherapy given the fact that HIV is an exclusion criteria from clinical trials, and thus the outcomes and drug interactions in the presence of HAART are unknown [132–134].

It is estimated that the risk of developing lung cancer in HIV patients is 2–6 times higher than the average population [131]. The incidence of lung cancer in the HIV patient is on the rise for several reasons. First, they are more vulnerable to developing lung cancer because of their reduced immune surveillance system [129, 130], pulmonary damage from repeated opportunistic infections, and (often) smoking [128, 129, 132]. Additionally, the use of HAART is enabling the HIV population to reach an age and/or cumulative exposure to tobacco smoke at which lung cancer may arise [129]. Interestingly, although the predicted risk of lung cancer in HIV was highest among intravenous drug users, females, and younger patients, the actual incidence of lung cancer was highest in males and the elderly [135].

Unlike malignant diseases like Non-Hodgkin's Lymphoma (NHL) and Kaposi Sarcoma (KS) which improve after immune reconstitution from antiretroviral therapy, multiple studies have shown that lung cancers do not respond to HAART, and absolute CD4 count does not correlate with risk or response to treatment [129, 135]. For this reason, although NHL and KS previously comprised 95 % of all malignancies found in the HIV population, this trend is expected to shift in the future as HAART effectively eliminates such disease states and allows HIV patients to live long enough to develop lung cancer [129]. A recent study by Makinson et al. also suggests that HAART may actually interfere with the efficacy of antineoplastic regimens [133], although most other studies have not found any evidence of benefit or detriment to concurrent usage beyond higher risk of drug toxicities [132].

Currently, evidence regarding outcomes of lung cancer in HIV patients suggests they are uniformly poor. It is unclear at this point whether their worse survival is due

to AIDS-related complications, advanced stage at diagnosis due to a more aggressive form of cancer, increased treatment toxicity and/or inefficacy, or lack of therapy [131].

Studies have shown that patients with HIV receive cancer treatment less frequently than patients without HIV and have a correspondingly higher mortality rate [131]. Even after adjustment for multiple covariates, there is a bias toward withholding care in HIV patients, including potentially curative surgery for early stage disease. For more advanced stages, there may be an issue of provider reluctance to treat patients with chemotherapy who are already on multiple other toxic drugs, given the absence of any clinical trial data on safety and efficacy in HIV patients [130, 131]. Misclassification of patients may also contribute to inappropriate treatment. When used to assess for extent of tumor burden in HIV patients, PET-CT scans may inadvertently and inappropriately upstage the patient if no confirmatory biopsy is obtained. This is because HIV patients often have chronic inflammation and concurrent infections which may also be FDG-avid [132], thus confusing the issue.

In the past, most experts believed that lung cancer mortality was higher for HIV patients compared to their non-HIV cohorts. This may be due to the fact that HIV-infected patients frequently fall into a demographic that already puts them at higher risk of worse outcomes—i.e., they tend to be black and/or gay men with end-stage disease at the time of diagnosis of lung cancer—all of which are predictors of lower likelihood of treatment [131]. However, more recent studies in the era of HAART now demonstrate no difference in survival between HIV-infected patients and the general lung cancer population [130].

In regards to low-dose CT screening, lung cancer is diagnosed in HIV patients at a significantly younger median age—50 years compared with the 68 years for SEER participants overall [132]. This observation is important because these younger at-risk patients would not currently meet the USPSTF recommendations for indications for lung cancer screening. Some experts argue that the chances of finding incidental abnormalities are higher in the HIV population which may prompt unnecessary additional workup for lung cancer. However, a recent study by Sigel and colleagues showed that HIV patients with a CD4 count greater than 200 do not have a significantly higher rate of nonmalignant pulmonary lesions detected on screening CT scan compared to non-HIV patients. Therefore, the risk–benefit ratio may be favorable for screening less immunosuppressed HIV patients for lung cancer using low-dose CT scans at an earlier age, but further studies are needed to better understand the trade-offs [134].

For lung cancer disparities based on age and comorbidities (including HIV) to be resolved, a major shift in clinicians' attitudes must occur. They must understand that older adults and patients with chronic comorbidities are not necessarily as frail as they believe, and new advances in surgery, delivery of radiation, and chemotherapy may provide less toxic treatment options in the future. For evidence-based guidelines to adequately reflect these changes, a radical shift in clinical trial design must also occur. Enrollment of more patients with advanced age, HIV, and other significant comorbidities must be considered to generate study results that are more applicable to real-life conditions. Finally, given the mortality benefit of low-dose CT scans in lung cancer detection, the criteria for screening should be expanded to encompass a larger expanse of at-risk populations, including HIV and the extremes of age.

Conclusions

When discussing disparities in lung cancer, a quote by Arthur Schlesinger sums it up best by underscoring the fact that "science and technology [may] revolutionize our lives, but memory, tradition, and myth frame our response." No matter what kind of modern miracles medicine may offer, the social paradigms in America will ultimately define what kind of impact they achieve in regards to lung cancer outcomes.

Despite attempts at eliminating inequities based on race, education, or income, there remain persistent barriers to the optimal prevention, diagnosis, and treatment of lung cancer that are differentially encountered by different populations. The intricate web which interconnects them also captures other overlapping disparities such as higher smoking rates, insurance type (or lack of), and quality of hospital care.

Although provider discrimination is an easy target to blame as the cause of undertreatment in the disenfranchised, patient factors may also play a role. Lack of education, understanding, or cultural and communication difficulties may lead them to refuse or be poorly adherent with recommended care, even if it is freely offered.

Furthermore, the historical underrepresentation in clinical trials of members of minority groups, the elderly, and patients with significant comorbidities (including HIV), only compounds these disparities in lung cancer outcomes. Providers may be reluctant to prescribe guideline-appropriate treatment due to lack of information regarding safety and efficacy in a particular demographic group. Therefore, the elimination of disparities in lung cancer outcomes will require a combination of both social change and technological advancement. Potential targets include:

1. Tobacco prevention targeted at key risk groups, including adolescent girls as well as members of racial, ethnic, and sexual minority groups, to reduce the overall incidence of lung cancer.
2. Construction of parks, grocery stores, better public transportation, and primary care clinics within poverty-stricken communities to encourage healthier habits and routine medical visits.
3. Universal health care coverage, as well as standardization of practices across hospitals, to improve access to guideline-appropriate lung cancer care.
4. Physician training in cultural sensitivity to improve communication and patient trust and compliance.
5. Increased enrollment of underrepresented populations in clinical trials so that providers will no longer view HIV, age, and comorbidities as a reason not to treat.
6. Appreciation of the complexity of lung cancer biology, including gender differences and genetic mutations, leading to more targeted, effective, and personalized therapy.

Only when social, behavioral, cultural, and biological differences are acknowledged, understood, and corrected will lung cancer prognosis and disparities in outcomes truly improve.

References

1. Williams DR, et al. Integrating multiple social statuses in health disparities research: the case of lung cancer. Health Serv Res. 2012;47:1255–77. doi:10.1111/j.1475-6773.2012.01404.x.
2. Unequal treatment: confronting racial and ethnic disparities in health care (full printed version). Washington, DC: The National Academies Press; 2003.
3. Forrest LF, Adams J, Wareham H, Rubin G, White M. Socioeconomic inequalities in lung cancer treatment: systematic review and meta-analysis. PLoS Med. 2013;10:e1001376. doi:10.1371/journal.pmed.1001376.
4. Erhunmwunsee L, Joshi MB, Conlon DH, Harpole Jr DH. Neighborhood-level socioeconomic determinants impact outcomes in nonsmall cell lung cancer patients in the Southeastern United States. Cancer. 2012;118:5117–23. doi:10.1002/cncr.26185.
5. Herd P, Goesling B, House JS. Socioeconomic position and health: the differential effects of education versus income on the onset versus progression of health problems. J Health Soc Behav. 2007;48:223–38.
6. Yang R, et al. Do racial or socioeconomic disparities exist in lung cancer treatment? Cancer. 2010;116:2437–47. doi:10.1002/cncr.24986.
7. Williams DR, Collins C. Racial residential segregation: a fundamental cause of racial disparities in health. Public Health Rep. 2001;116:404–16.
8. Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. Ann N Y Acad Sci. 2010;1186:69–101. doi:10.1111/j.1749-6632.2009.05339.x.
9. Ward E, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin. 2004;54:78–93.
10. Potosky AL, Saxman S, Wallace RB, Lynch CF. Population variations in the initial treatment of non-small-cell lung cancer. J Clin Oncol. 2004;22:3261–8. doi:10.1200/JCO.2004.02.051.
11. Bach PB, Cramer LD, Warren JL, Begg CB. Racial differences in the treatment of early-stage lung cancer. N Engl J Med. 1999;341:1198–205. doi:10.1056/NEJM199910143411606.
12. Haiman CA, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med. 2006;354:333–42. doi:10.1056/NEJMoa033250.
13. Kagawa-Singer M, Dadia AV, Yu MC, Surbone A. Cancer, culture, and health disparities: time to chart a new course? CA Cancer J Clin. 2010;60:12–39. doi:10.3322/caac.20051.
14. Margolis ML, et al. Racial differences pertaining to a belief about lung cancer surgery: results of a multicenter survey. Ann Intern Med. 2003;139:558–63.
15. Gordon HS, Street Jr RL, Sharf BF, Kelly PA, Souchek J. Racial differences in trust and lung cancer patients' perceptions of physician communication. J Clin Oncol. 2006;24:904–9. doi:10.1200/JCO.2005.03.1955.
16. Mulligan CR, et al. Unlimited access to care: effect on racial disparity and prognostic factors in lung cancer. Cancer Epidemiol Biomarkers Prev. 2006;15:25–31. doi:10.1158/1055-9965.EPI-05-0537.
17. Farjah F, et al. Racial disparities among patients with lung cancer who were recommended operative therapy. Arch Surg. 2009;144:14–8. doi:10.1001/archsurg.2008.519.
18. Hardy D, et al. Racial disparities and survival for nonsmall-cell lung cancer in a large cohort of black and white elderly patients. Cancer. 2009;115:4807–18. doi:10.1002/cncr.24521.
19. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. J Clin Oncol. 2006;24:413–8. doi:10.1200/JCO.2005.02.1758.
20. Bryant AS, Cerfolio RJ. Impact of race on outcomes of patients with non-small cell lung cancer. J Thorac Oncol. 2008;3:711–5. doi:10.1097/JTO.0b013e31817c60c7.
21. Berger M, Lund M, Brawley O. Racial disparities in lung cancer. Curr Probl Cancer. 2007;31:202–10. doi:10.1016/j.currproblcancer.2007.02.002.
22. Hede K. Drilling down to the causes of racial disparities in lung cancer. J Natl Cancer Inst. 2010;102:1385–7. doi:10.1093/jnci/djq371.

23. Park ER, Japuntich SJ, Traeger L, Cannon S, Pajolek H. Disparities between blacks and whites in tobacco and lung cancer treatment. Oncologist. 2011;16:1428–34. doi:10.1634/theoncologist.2011-0114.
24. Whooley MA, Boyd AL, Gardin JM, Williams DR. Religious involvement and cigarette smoking in young adults: the CARDIA study (Coronary Artery Risk Development in Young Adults) study. Arch Intern Med. 2002;162:1604–10.
25. Wallace Jr JM, Brown TN, Bachman JG, LaVeist TA. The influence of race and religion on abstinence from alcohol, cigarettes and marijuana among adolescents. J Stud Alcohol. 2003;64:843–8.
26. Dey AN, Lucas JW. Physical and mental health characteristics of U.S.- and foreign-born adults: United States, 1998-2003. Advance Data; 2006. p. 1–19.
27. Singh GK, Miller BA. Health, life expectancy, and mortality patterns among immigrant populations in the United States. Can J Public Health. 2004;95:I14–21.
28. Clegg LX, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control. 2009;20:417–35. doi:10.1007/s10552-008-9256-0.
29. Lin JJ, Mhango G, Wall MM, Lurslurchachai L, Bond KT, Nelson JE, Berman AR, Salazar-Schicchi J, Powell C, Keller SM, Halm EA, Leventhal H, Wisnivesky JP. Cultural factors associated with racial disparities in lung cancer care. Ann Am Thorac Soc. 2014;11:489–95. doi:10.1513/AnnalsATS.201402-055OC.
30. Suga JM, et al. Racial disparities on the use of invasive and noninvasive staging in patients with non-small cell lung cancer. J Thorac Oncol. 2010;5:1772–8. doi:10.1097/JTO.0b013e3181f69f22.
31. McCann J, et al. Evaluation of the causes for racial disparity in surgical treatment of early stage lung cancer. Chest. 2005;128:3440–6. doi:10.1378/chest.128.5.3440.
32. Mehta RS, Lenzner D, Argiris A. Race and health disparities in patient refusal of surgery for early-stage non-small cell lung cancer: a SEER cohort study. Ann Surg Oncol. 2012;19:722–7. doi:10.1245/s10434-011-2087-3.
33. Cykert S, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. JAMA. 2010;303:2368–76. doi:10.1001/jama.2010.793.
34. Persky S, Kaphingst KA, Allen Jr VC, Senay I. Effects of patient-provider race concordance and smoking status on lung cancer risk perception accuracy among African-Americans. Ann Behav Med. 2013;45:308–17. doi:10.1007/s12160-013-9475-9.
35. Hardy D, Chan W, Liu C, Cormier J, Xia R, Bruera E, Du X. Racial disparities in the use of hospice services according to geographic residence and socioeconomic status in an elderly cohort with nonsmall cell lung cancer. Cancer. 2011;117:1506–15. doi:10.1002/cncr.25669.
36. U.S. Census Bureau. Current population reports consumer income P60. Washington, DC: Bureau of the Census. 2009
37. Wilper AP, et al. Health insurance and mortality in US adults. Am J Public Health. 2009;99:2289–95. doi:10.2105/AJPH.2008.157685.
38. Slatore CG, Au DH, Gould MK, American Thoracic Society Disparities in Healthcare Group. An official American Thoracic Society systematic review: insurance status and disparities in lung cancer practices and outcomes. Am J Respir Crit Care Med. 2010;182:1195–205. doi:10.1164/rccm.2009-038ST.
39. Virgo KS, et al. Safety-net burden hospitals and likelihood of curative-intent surgery for non-small cell lung cancer. J Am Coll Surg. 2011;213:633–43. doi:10.1016/j.jamcollsurg.2011.07.014.
40. Bradley CJ, Given CW, Roberts C. Disparities in cancer diagnosis and survival. Cancer. 2001;91:178–88.
41. Bradley CJ, Given CW, Dahman B, Luo Z, Virnig BA. Diagnosis of advanced cancer among elderly Medicare and Medicaid patients. Med Care. 2007;45:410–9. doi:10.1097/01.mlr.0000256970.19359.2a.
42. Bradley CJ, Gardiner J, Given CW, Roberts C. Cancer, Medicaid enrollment, and survival disparities. Cancer. 2005;103:1712–8. doi:10.1002/cncr.20954.

43. Bradley CJ, Dahman B, Given CW. Treatment and survival differences in older Medicare patients with lung cancer as compared with those who are dually eligible for Medicare and Medicaid. J Clin Oncol. 2008;26:5067–73. doi:10.1200/JCO.2008.16.3071.
44. Shugarman LR, Sorbero ME, Tian H, Jain AK, Ashwood JS. An exploration of urban and rural differences in lung cancer survival among medicare beneficiaries. Am J Public Health. 2008;98:1280–7. doi:10.2105/AJPH.2006.099416.
45. Cheung MC, et al. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. Ann Surg Oncol. 2009;16:3–13. doi:10.1245/s10434-008-0025-9.
46. Roetzheim RG, et al. Managed care and cancer outcomes for Medicare beneficiaries with disabilities. Am J Manag Care. 2008;14:287–96.
47. Greenberg ER, et al. Social and economic factors in the choice of lung cancer treatment. A population-based study in two rural states. N Engl J Med. 1988;318:612–7. doi:10.1056/NEJM198803103181006.
48. Esnaola NF, et al. Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. Ann Thorac Surg. 2008;86:220–6; discussion 227. doi:10.1016/j.athoracsur.2008.02.072.
49. Harlan LC, et al. Insurance status and the use of guideline therapy in the treatment of selected cancers. J Clin Oncol. 2005;23:9079–88. doi:10.1200/JCO.2004.00.1297.
50. Groth SS, et al. Effect of insurance status on the surgical treatment of early-stage non-small cell lung cancer. Ann Thorac Surg. 2013;95:1221–6. doi:10.1016/j.athoracsur.2012.10.079.
51. Yorio JT, Yan J, Xie Y, Gerber DE. Socioeconomic disparities in lung cancer treatment and outcomes persist within a single academic medical center. Clin Lung Cancer. 2012;13:448–57. doi:10.1016/j.cllc.2012.03.002.
52. Lathan CS, Neville BA, Earle CC. Racial composition of hospitals: effects on surgery for early-stage non-small-cell lung cancer. J Clin Oncol. 2008;26:4347–52. doi:10.1200/JCO.2007.15.5291.
53. Bach PB, et al. The influence of hospital volume on survival after resection for lung cancer. N Engl J Med. 2001;345:181–8. doi:10.1056/NEJM200107193450306.
54. Goodney PP, Lucas FL, Stukel TA, Birkmeyer JD. Surgeon specialty and operative mortality with lung resection. Ann Surg. 2005;241:179–84.
55. Neighbors CJ, et al. Ethnic/racial disparities in hospital procedure volume for lung resection for lung cancer. Med Care. 2007;45:655–63. doi:10.1097/MLR.0b013e3180326110.
56. Paggi MG, Vona R, Abbruzzese C, Malorni W. Gender-related disparities in non-small cell lung cancer. Cancer Lett. 2010;298:1–8. doi:10.1016/j.canlet.2010.08.009.
57. Patel JD, Bach PB, Kris MG. Lung cancer in US women: a contemporary epidemic. JAMA. 2004;291:1763–8. doi:10.1001/jama.291.14.1763.
58. Ramchandran K, Patel JD. Sex differences in susceptibility to carcinogens. Semin Oncol. 2009;36:516–23. doi:10.1053/j.seminoncol.2009.09.005.
59. Belani CP, Marts S, Schiller J, Socinski MA. Women and lung cancer: epidemiology, tumor biology, and emerging trends in clinical research. Lung Cancer. 2007;55:15–23. doi:10.1016/j.lungcan.2006.09.008.
60. Donington JS, Le QT, Wakelee HA. Lung cancer in women: exploring sex differences in susceptibility, biology, and therapeutic response. Clin Lung Cancer. 2006;8:22–9. doi:10.3816/CLC.2006.n.029.
61. Harichand-Herdt S, Ramalingam SS. Gender-associated differences in lung cancer: clinical characteristics and treatment outcomes in women. Semin Oncol. 2009;36:572–80. doi:10.1053/j.seminoncol.2009.10.007.
62. Donington JS, Colson YL. Sex and gender differences in non-small cell lung cancer. Semin Thorac Cardiovasc Surg. 2011;23:137–45. doi:10.1053/j.semtcvs.2011.07.001.
63. Pauk N, Kubik A, Zatloukal P, Krepela E. Lung cancer in women. Lung Cancer. 2005;48:1–9. doi:10.1016/j.lungcan.2004.10.009.
64. Planchard D, Loriot Y, Goubar A, Commo F, Soria JC. Differential expression of biomarkers in men and women. Semin Oncol. 2009;36:553–65. doi:10.1053/j.seminoncol.2009.09.004.

65. Henschke CI, Miettinen OS. Women's susceptibility to tobacco carcinogens. Lung Cancer. 2004;43:1–5.
66. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst. 1996;88:183–92.
67. Asomaning K, et al. Second hand smoke, age of exposure and lung cancer risk. Lung Cancer. 2008;61:13–20. doi:10.1016/j.lungcan.2007.11.013.
68. Clement-Duchene C, et al. Characteristics of never smoker lung cancer including environmental and occupational risk factors. Lung Cancer. 2010;67:144–50. doi:10.1016/j.lungcan.2009.04.005.
69. Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. Chest. 2005;128:370–81. doi:10.1378/chest.128.1.370.
70. Fu JB, Kau TY, Severson RK, Kalemkerian GP. Lung cancer in women: analysis of the national Surveillance, Epidemiology, and End Results database. Chest. 2005;127:768–77. doi:10.1378/chest.127.3.768.
71. Hsu LH, et al. Sex-associated differences in non-small cell lung cancer in the new era: is gender an independent prognostic factor? Lung Cancer. 2009;66:262–7. doi:10.1016/j.lungcan.2009.01.020.
72. Bronte G, et al. Driver mutations and differential sensitivity to targeted therapies: a new approach to the treatment of lung adenocarcinoma. Cancer Treat Rev. 2010;36 Suppl 3:S21–9. doi:10.1016/S0305-7372(10)70016-5.
73. Li YJ, Tsai YC, Chen YC, Christiani DC. Human papilloma virus and female lung adenocarcinoma. Semin Oncol. 2009;36:542–52. doi:10.1053/j.seminoncol.2009.10.002.
74. Gatzemeier U, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol. 2004;15:19–27.
75. Chlebowski RT, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet. 2009;374:1243–51. doi:10.1016/S0140-6736(09)61526-9.
76. Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A. Hormone replacement therapy is associated with decreased survival in women with lung cancer. J Clin Oncol. 2006;24:59–63. doi:10.1200/JCO.2005.02.9827.
77. Siegfried JM, Hershberger PA, Stabile LP. Estrogen receptor signaling in lung cancer. Semin Oncol. 2009;36:524–31. doi:10.1053/j.seminoncol.2009.10.004.
78. Bouchardy C, et al. Lung cancer mortality risk among breast cancer patients treated with antiestrogens. Cancer. 2011;117:1288–95. doi:10.1002/cncr.25638.
79. Nose N, Uramoto H, Iwata T, Hanagiri T, Yasumoto K. Expression of estrogen receptor beta predicts a clinical response and longer progression-free survival after treatment with EGFR-TKI for adenocarcinoma of the lung. Lung Cancer. 2011;71:350–5. doi:10.1016/j.lungcan.2010.06.009.
80. Stabile LP, et al. Combined targeting of the estrogen receptor and the epidermal growth factor receptor in non-small cell lung cancer shows enhanced antiproliferative effects. Cancer Res. 2005;65:1459–70. doi:10.1158/0008-5472.CAN-04-1872.
81. Traynor AM, et al. Pilot study of gefitinib and fulvestrant in the treatment of post-menopausal women with advanced non-small cell lung cancer. Lung Cancer. 2009;64:51–9. doi:10.1016/j.lungcan.2008.07.002.
82. Lord RV, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res. 2002;8:2286–91.
83. Mok TS, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57. doi:10.1056/NEJMoa0810699.
84. Maemondo M, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380–8. doi:10.1056/NEJMoa0909530.
85. Nelson HH, et al. Implications and prognostic value of K-ras mutation for early-stage lung cancer in women. J Natl Cancer Inst. 1999;91:2032–8.
86. Boehmer U, Miao X, Ozonoff A. Cancer survivorship and sexual orientation. Cancer. 2011;117:3796–804. doi:10.1002/cncr.25950.

87. Pizacani BA, et al. Smoking-related knowledge, attitudes and behaviors in the lesbian, gay and bisexual community: a population-based study from the U.S. Pacific Northwest. Prev Med. 2009;48:555–61. doi:10.1016/j.ypmed.2009.03.013.
88. Bonvicini KA, Perlin MJ. The same but different: clinician-patient communication with gay and lesbian patients. Patient Educ Couns. 2003;51:115–22.
89. Wallick MM, Cambre KM, Townsend MH. How the topic of homosexuality is taught at U.S. medical schools. Acad Med. 1992;67:601–3.
90. Ryan H, Wortley PM, Easton A, Pederson L, Greenwood G. Smoking among lesbians, gays, and bisexuals: a review of the literature. Am J Prev Med. 2001;21:142–9.
91. Lee JG, Griffin GK, Melvin CL. Tobacco use among sexual minorities in the USA, 1987 to May 2007: a systematic review. Tob Control. 2009;18:275–82. doi:10.1136/tc.2008.028241.
92. Weinmann M, Jeremic B, Toomes H, Friedel G, Bamberg M. Treatment of lung cancer in the elderly. Part I: non-small cell lung cancer. Lung Cancer. 2003;39:233–53.
93. Gridelli C, Langer C, Maione P, Rossi A, Schild SE. Lung cancer in the elderly. J Clin Oncol. 2007;25:1898–907. doi:10.1200/JCO.2006.10.3085.
94. Pallis AG, Scarci M. Are we treating enough elderly patients with early stage non-small cell lung cancer? Lung Cancer. 2011;74:149–54. doi:10.1016/j.lungcan.2011.05.025.
95. Quoix E, Westeel V, Zalcman G, Milleron B. Chemotherapy in elderly patients with advanced non-small cell lung cancer. Lung Cancer. 2011;74:364–8. doi:10.1016/j.lungcan.2011.06.006.
96. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013;5:3–29. doi:10.2147/CLEP.S47150.
97. Kumar A, Soares HP, Balducci L, Djulbegovic B, National Cancer Institute. Treatment tolerance and efficacy in geriatric oncology: a systematic review of phase III randomized trials conducted by five National Cancer Institute-sponsored cooperative groups. J Clin Oncol. 2007;25:1272–6. doi:10.1200/JCO.2006.09.2759.
98. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341:2061–7. doi:10.1056/NEJM199912303412706.
99. Lewis JH, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21:1383–9.
100. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol. 2004;22:4626–31. doi:10.1200/JCO.2004.02.175.
101. Dale DC. Poor prognosis in elderly patients with cancer: the role of bias and undertreatment. J Support Oncol. 2003;1:11–7.
102. Fentiman IS, et al. Cancer in the elderly: why so badly treated? Lancet. 1990;335:1020–2.
103. Rijke JM, et al. Influence of age, comorbidity and performance status on the choice of treatment for patients with non-small cell lung cancer; results of a population-based study. Lung Cancer. 2004;46:233–45. doi:10.1016/j.lungcan.2004.03.011.
104. Port JL, et al. Surgical resection for lung cancer in the octogenarian. Chest. 2004;126:733–8. doi:10.1378/chest.126.3.733.
105. Mery CM, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest. 2005;128:237–45. doi:10.1378/chest.128.1.237.
106. Pallis AG, et al. EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population. Ann Oncol. 2010;21:692–706. doi:10.1093/annonc/mdp360.
107. Lim E, et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010;65 Suppl 3:iii1–27. doi:10.1136/thx.2010.145938.
108. Kamiyoshihara M, Kawashima O, Ishikawa S, Morishita Y. Long-term results after pulmonary resection in elderly patients with non-small cell lung cancer. J Cardiovasc Surg. 2000;41:483–6.

109. Goodgame B, et al. Risk of recurrence of resected stage I non-small cell lung cancer in elderly patients as compared with younger patients. J Thorac Oncol. 2009;4:1370–4. doi:10.1097/JTO.0b013e3181b6bc1b.
110. Groth SS, et al. Conditional cancer-specific versus cardiovascular-specific survival after lobectomy for stage I non-small cell lung cancer. Ann Thorac Surg. 2010;90:375–82. doi:10.1016/j.athoracsur.2010.04.100.
111. Fruh M, et al. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. J Clin Oncol. 2008;26:3573–81. doi:10.1200/JCO.2008.16.2727.
112. Dyszkiewicz W, Pawlak K, Gasiorowski L. Early post-pneumonectomy complications in the elderly. Eur J Cardiothorac Surg. 2000;17:246–50.
113. Meerbeeck JP, Damhuis RA, Vos de Wael ML. High postoperative risk after pneumonectomy in elderly patients with right-sided lung cancer. Eur Respir J. 2002;19:141–5.
114. Sullivan V, et al. Advanced age does not exclude lobectomy for non-small cell lung carcinoma. Chest. 2005;128:2671–6. doi:10.1378/chest.128.4.2671.
115. Balduyck B, Hendriks J, Lauwers P, Sardari Nia P, Van Schil P. Quality of life evolution after lung cancer surgery in septuagenarians: a prospective study. Eur J Cardiothorac Surg. 2009;35:1070–5; discussion 1075. doi:10.1016/j.ejcts.2009.01.050.
116. Okami J, et al. Pulmonary resection in patients aged 80 years or over with clinical stage I non-small cell lung cancer: prognostic factors for overall survival and risk factors for postoperative complications. J Thorac Oncol. 2009;4:1247–53. doi:10.1097/JTO.0b013e3181ae285d.
117. Pepe C, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol. 2007;25:1553–61. doi:10.1200/JCO.2006.09.5570.
118. Quoix E, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet. 2011;378:1079–88. doi:10.1016/S0140-6736(11)60780-0.
119. Tsukada H, et al. Randomized controlled trial comparing docetaxel (D)-cisplatin (P) combination with D alone in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC): JCOG0207. J Clin Oncol. 2007;25:7629.
120. Shepherd FA, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353:123–32. doi:10.1056/NEJMoa050753.
121. Jackman DM, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol. 2007;25:760–6. doi:10.1200/JCO.2006.07.5754.
122. Haasbeek CJ, Lagerwaard FJ, Antonisse ME, Slotman BJ, Senan S. Stage I nonsmall cell lung cancer in patients aged > or =75 years: outcomes after stereotactic radiotherapy. Cancer. 2010;116:406–14. doi:10.1002/cncr.24759.
123. Vinod SK, Sidhom MA, Gabriel GS, Lee MT, Delaney GP. Why do some lung cancer patients receive no anticancer treatment? J Thorac Oncol. 2010;5:1025–32. doi:10.1097/JTO.0b013e3181da85e4.
124. Janssen-Heijnen ML, Schipper RM, Razenberg PP, Crommelin MA, Coebergh JW. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. Lung Cancer. 1998;21:105–13.
125. Gronberg BH, et al. Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy. Eur J Cancer. 2010;46:2225–34. doi:10.1016/j.ejca.2010.04.009.
126. Onega T, et al. Influence of NCI cancer center attendance on mortality in lung, breast, colorectal, and prostate cancer patients. Med Care Res Rev. 2009;66:542–60. doi:10.1177/1077558709335536.
127. Rueth NM, et al. Surgical treatment of lung cancer: predicting postoperative morbidity in the elderly population. J Thorac Cardiovasc Surg. 2012;143:1314–23. doi:10.1016/j.jtcvs.2011.09.072.

128. Aboulafia DM. Decision making in non-AIDS-defining malignancies. Lancet Oncol. 2012;13:1172–3. doi:10.1016/S1470-2045(12)70520-X.
129. Bower M, et al. HIV-related lung cancer in the era of highly active antiretroviral therapy. AIDS. 2003;17:371–5. doi:10.1097/01.aids.0000050788.28043.cf.
130. Rengan R, Mitra N, Liao K, Armstrong K, Vachani A. Effect of HIV on survival in patients with non-small-cell lung cancer in the era of highly active antiretroviral therapy: a population-based study. Lancet Oncol. 2012;13:1203–9. doi:10.1016/S1470-2045(12)70466-7.
131. Suneja G, et al. Disparities in the treatment and outcomes of lung cancer among HIV-infected individuals. AIDS. 2013;27:459–68. doi:10.1097/QAD.0b013e32835ad56e.
132. D'Jaen GA, et al. Human immunodeficiency virus-associated primary lung cancer in the era of highly active antiretroviral therapy: a multi-institutional collaboration. Clin Lung Cancer. 2010;11:396–404. doi:10.3816/CLC.2010.n.051.
133. Makinson A, Pujol JL, Le Moing V, Peyriere H, Reynes J. Interactions between cytotoxic chemotherapy and antiretroviral treatment in human immunodeficiency virus-infected patients with lung cancer. J Thorac Oncol. 2010;5:562–71. doi:10.1097/JTO.0b013e3181d3ccf2.
134. Sigel K, Wisnivesky J, Shahrir S, Brown S, Justice A, Kim J, Rodriguez-Barradas M, Akgun K, Rimland D, Soo Hoo G, Crothers K. Findings in asymptomatic HIV-infected patients undergoing chest computed tomography testing: implications for lung cancer screening. AIDS. 2014;28:1007–14, doi:10.1097/QAD.0000000000000189.
135. Hou W, Fu J, Ge Y, Du J, Hua S. Incidence and risk of lung cancer in HIV-infected patients. J Cancer Res Clin Oncol. 2013;139:1781–94. doi:10.1007/s00432-013-1477-2.

Chapter 13
Health Disparities in Critical Illness

Daniel Monroy Chaves and John Daryl Thornton

Key Points

- Health disparities are well described in most facets of critical illness.
- Racial and ethnic disparities are the most commonly described disparities in critical illness.
- However, race and ethnicity are often used as substitutes for other factors such as geographic location of residence or geographic location for receipt of health care that have an equal or greater effect on patient outcomes.
- Studies exploring the effects of specific health disparities (such as race and ethnicity) on outcomes of the critically ill need to account for as many additional factors as possible that may be involved in order to give a more detailed and accurate picture of the true factors affecting patient outcomes.
- Novel approaches to the design and evaluation of targeted interventions are needed to eliminate health disparities in critical illness.

D.M. Chaves, M.D.
Division of Pulmonary, Critical Care, and Sleep Medicine, The MetroHealth Campus of Case Western Reserve University, Cleveland, OH, USA

J.D. Thornton, M.D., M.P.H. (✉)
Division of Pulmonary, Critical Care, and Sleep Medicine and Center for Reducing Health Disparities, The MetroHealth Campus of Case Western Reserve University, Cleveland, OH 44109, USA
e-mail: daryl.thornton@case.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_13

Background

The foundation for our current understanding of the practice of critical care medicine and the need for dedicated areas to care for the critically ill can be traced to Kommunehospitalet, the municipal hospital of Copenhagen, Denmark in 1953 [1]. The polio epidemic had ravaged the country and hospitals had exceeded their ability to care for those with respiratory failure [2]. Dr. Bjorn Ibsen, an anesthesiologist, not only described successful practices in the care of such patients, but he also conceived of a "special department, where they were under constant observation by a team, consulting epidemiologist, the ear, nose, and throat surgeon, and the anaesthetist, all working with help from an excellent and capable laboratory" [3]. Today, outcomes continue to be most favorable among critically ill patients that are cared for in an intensive care unit (ICU) and by a multidisciplinary care team with significant experience in dealing with such patients [4–6]. However, such care is resource exhaustive and relatively scarce. With an aging American population, the need for critical care services over the next few decades will likely dramatically increase, while the numbers of trained intensivists and pulmonologists will decrease below current levels [7, 8]. Many ICUs are already facing rapid increases in occupancy, having recently reached an alarming average occupancy of 68 %, leaving little room for the projected increases or for more acute needs in the setting of a pandemic [9, 10]. ICUs already buckling under the significant strain from the current increased demands for their services may not be able to sufficiently care for additional patients, which may lead to an increase in morbidity and mortality [11, 12]. Limited availability of critical care services will likely have the greatest impact among those who are most vulnerable and may lead to an increase in health disparities [13].

Research in health disparities related to critical illness has largely reflected health disparities research involving other aspects of medicine [14, 15] with early research being mostly descriptive (Table 13.1) [16, 17]. These descriptive studies established the prevalence of disparities in critical care and identified potential benchmarks for improvement. The next phase in health disparities research involved identifying the underlying mechanisms responsible for the described disparities. This has afforded us a deeper understanding of the root causes of health disparities, thereby assisting in the development of the third phase of research—evaluation of targeted interventions to eliminate health disparities. Unfortunately, this phase of health disparities research has been slow to evolve and is clearly where most of the work is needed [18]. This chapter provides a broad overview of health disparities in critical care and identifies mechanisms for the development and testing of novel disparities-related interventions. Gaps in our current understanding and areas of future need are emphasized (Table 13.2).

Table 13.1 State of health disparities research in critical care

Critical care settings	Descriptive studies	Mechanistic studies	Interventional studies
Emergency Department	*	_	_
Cardiac Critical Care	**	*	_
Medical Critical Care	***	**	_
Neurologic Critical Care	***	**	_
Surgical Critical Care	***	*	_

Table 13.2 Challenges and recommendations to further exploration of health disparities in critical illness

Challenge	Recommendation
1. Lack of clear guidelines regarding integral components of health disparities publications	Development of evidence-based guidelines and author checklists for health disparities publications
2. Racial and ethnic categories are static and mutually exclusive	Allow study participants to self-identify as many racial and ethnic categories as desired
3. Factors confounding racial, ethnic, age, and gender disparities are often missing	Aim to address all known factors affecting the relationship between disparities and health outcomes
4. Too few mechanistic and interventional studies	1. Creation of funding mechanisms devoted to exploring novel means to alleviate health disparities
	2. Increase in exposure of young investigators to health disparities research

Some Words About Race…

Racial disparities are perhaps the most studied aspect of health disparities, and differences in outcomes by race are well reported [15]. Osborn and Feit delineated the confusion associated with using race as a variable in research [19]. The common assumption in many studies is that the results reflect biological or genetic differences attributed to race. However, these studies often fail to account for the individual and societal complexities and lack of well-defined boundaries between the socially defined constructs of race and ethnicity [20]. Researchers have used race as a substitute for socioeconomic status, culture, and class, as well as genetic and ancestry-based biological constructs. With such wide variability in the definition, it is not surprising that study findings have been so disparate. To confound measures further, the assessment of race is also variable, ranging from direct observation to surrogate report, or by the optimal (unbiased and most detailed) method, self-report. Even well-regarded sources of data including the U.S. Census, state birth and death

certificates, and hospital and payer records have substantial variability in the collection and ascertainment of race, despite the presence of federal guidelines [21]. Researchers reporting results of racial disparities are encouraged to be transparent and thorough in their assessment of race and include confounding factors that are commonly associated with race and adverse outcomes in their studies (see section "Factors Confounding Racial, Ethnic, Age, and Gender Disparities" below). In turn, readers of health disparities studies are encouraged to interpret the study results in the context of the information provided regarding the characterization of race. In this chapter, we have provided study results along with linking contextual information to promote a clearer understanding of the association between race and adverse outcomes among the critically ill.

Types of Health Disparities Affecting the Critically Ill

Race and Ethnicity

African Americans are more likely to be admitted into the ICU presumably due to a higher prevalence of conditions requiring critical care, a higher severity of illness, and an increased number of comorbid conditions that complicate management [22–24]. For example, African American men may be at greater risk for the development of sepsis from Grampositive bacteria and to have at least one acute organ dysfunction upon presentation compared to whites [25]. Using the New Jersey inpatient database, Dombrovskiy et al. found that African American adults with sepsis were younger, had more comorbid conditions, and were more likely to be admitted into the ICU compared to whites [26]. In a cohort study using data from the Acute Respiratory Distress Syndrome Network, African American patients with ARDS had the greatest severity of critical illness and were more likely to have complicating comorbidities such as HIV, end-stage renal disease, or cirrhosis [23]. After adjusting for demographic and clinical factors, African Americans and Hispanics with ARDS had a higher mortality rate compared to non-Hispanic whites with ARDS. However, after adjusting for severity of illness, African American race was no longer associated with mortality while the relationship between Hispanic ethnicity and mortality persisted.

A similar trend of increased ICU admission is seen in the pediatric population. However, the reasons for it may not be as clear as in adults. In a study of 4676 pediatric ICU admissions in Shelby County, Tennessee, African American children were more likely to be admitted to the pediatric ICU compared to non-Hispanic white children of similar severity of critical illness (OR: 2.1, 95 % CI: 1.7–2.7) [27]. Interestingly, full-term African American children had higher risks of admission compared to full-term white children (OR: 1.8, 95 % CI: 1.3–2.5) but there was no difference in risk for admission between preterm African American and preterm white children (OR: 1.4; 95 % CI: 0.9–2.2). In the region where the study was conducted, African Americans have a significantly higher prevalence of preterm births

(0.1 compared to 0.06 for non-Hispanic whites). Once admitted into the ICU, there was no difference in mortality between full-term African American and white children (4 % vs. 6 %, $p=0.2$) or preterm African American and white children (6.8 % vs. 8.9 %, $p=0.5$). The authors posit that African American children, particularly those with special needs, are less likely to receive primary care and therefore are more likely to be admitted to the ICU with exacerbations of unmanaged or undermanaged diseases [28–30]. A better understanding of factors affecting ICU admission and outcomes in the pediatric population is needed.

Once admitted into an ICU, African American patients receive disparate care compared to whites, despite no ultimate difference in mortality. In a study of over 15,000 patients admitted to one of 42 ICUs in 40 hospitals, Williams et al. found that African Americans received less technological monitoring, less laboratory testing, and less life-supporting treatments within the first 24 h following admission compared to whites. Adjusted ICU lengths of stay were also shorter [31]. Rapoport et al. found that critically ill African Americans of similar severity of illness to whites received fewer pulmonary artery catheters [32].

There are also ethnic barriers to optimal critical care. Limited English proficiency is a facet of ethnic disparities that has received a considerable amount of recent attention due to the alarming frequency of associated adverse outcomes including delayed care, permanent disability, or even death [33–36]. Some of the most influential factors associated with these poor outcomes include miscommunication, lack of cultural understanding, and poor social support. During the ICU family conference, patients' surrogates with limited English proficiency may receive less information regarding their loved one's current illness and proposed treatment and less emotional support from caregivers despite the presence of professional interpreters [37, 38]. It appears that the presence of interpreters attenuates but does not eliminate these adverse outcomes to patients with limited English proficiency [39, 40]. However, some data suggest that outcomes among patients with limited English proficiency may be equal to or better than those of English proficient patients. In a large cohort study of patients admitted to the ICU of two Boston hospitals between 1997 and 2007, patients whose primary language was not English had 31 % lower odds of 30-day mortality compared to patients whose primary language was English [41].

Age

Currently, patients older than 65 years of age comprise 56 % of all ICU days and patients older than 85 years of age comprise 14 % [7, 42]. With the population continuing to age, this percentage is expected to increase [43]. Using prospective data from Australian and New Zealand ICUs, Bagshaw et al. predicted that by 2015 the rate of patients 80 years of age and older will increase by 72 % to approximately 1 in 4 ICU admissions [44].

Milbrandt et al. posited that aging "predisposes to critical illness due to lifelong accumulation of molecular and cellular damage leading to decreased physiologic reserves and leaving the individual less able to respond to stressors" [43]. Therefore, it is not surprising that increasing age is positively associated with increasing mortality. In Bagshaw's study, patients 80 years of age and older had an adjusted odds of ICU and hospital mortality significantly higher than patients between the ages of 18 and 40 (OR: 2.7, 95 % CI: 2.4–3, and OR: 5.4, 95 % CI: 4.9–5.9, respectively). Factors associated with the higher odds of death among patients 80 and older included admission from a chronic care facility, nonsurgical admission, need for mechanical ventilation, comorbid conditions, a longer ICU stay, and a higher severity of illness. However, despite the increased odds of mortality compared to younger patients, approximately 80 % of patients 80 years of age and older survived to hospital discharge. In a cohort study spanning 7 years of ICU patients admitted to a single academic center in Massachusetts, patients over the age of 65 represented more than 45 % of the total ICU population. Mortality (28-day and 1-year) increased with age despite adjustment for gender, comorbidities, severity of critical illness, and presence of do not resuscitate orders [45].

Severe sepsis, a frequent cause of ICU stay and mortality, has enjoyed an increased survival rate over the last decade. Some have attributed the increase to a change in the age distribution or case fatality rate among those affected. Using a cohort of fee-for-service Medicare beneficiaries aged 65 and older, Iwashyna et al. found that the number of incident 3-year survivors of severe sepsis rose 119 % between 1999 and 2008. They attributed this increase in survivorship to an increased rate of organ dysfunction per patient hospitalized with infection rather than a change in the age distribution or better survival among patients. In fact, the 3-year case-fatality rates only decreased from 73 to 71 % over the period of analysis [46].

With the majority of older individuals surviving a hospitalization for severe sepsis, a new problem has emerged—that of chronic disability. Prospective data of 470 patients with severe sepsis admitted to 24 ICUs in Finland revealed a 2-year mortality of 45 % and a lower quality of life compared to age- and sex-adjusted reference values without sepsis [47]. The 2-year mortality was 35 % among those patients older than 55 years of age compared to younger patients (9.8 %, $p<0.001$). As age increased, quality of life decreased, while the mean estimated cost per quality-adjusted life year (QALY) increased ranging from 325€ for those less than 24 years of age to 12,452€ for those over 81 years of age. The findings of significantly impaired quality of life following hospitalization and increased long-term mortality rates were confirmed in a 2010 systematic review of 30 studies [48]. The severity and duration of impairment was well delineated in another study by Iwashyna et al. They prospectively examined participants from the Health and Retirement Study whose data were linked with the Medicare database [49]. The prevalence of moderate to severe cognitive impairment was 11 % greater among the patients who had

been hospitalized for severe sepsis compared to those who had been hospitalized for other conditions. Impairments in cognitive and physical functioning persisted for at least 8 years following hospitalization, suggesting that many patients may be unable to ever return to independent functioning.

Despite the fact that the majority of critically ill older patients survive hospitalization, age-related barriers to ICU admission appear to exist. In a prospective cohort study conducted in 15 French hospitals, 2646 patients of age 80 years and older were triaged in the emergency room. The authors used standardized admission criteria to determine patient eligibility for admission. Of the 1426 patients who met definite admission criteria, only 31 % were referred for ICU admission, and only 52 % of those referred were admitted [50]. Increasing age was an independent factor associated with no referral for ICU admission (OR: 1.04, 95 % CI: 1.02–1.07 for every 1 year increase). Another study demonstrated that once admitted into the ICU, elderly patients are less likely than younger patients to receive intensive treatments such as mechanical ventilation and renal replacement therapy, perhaps due to the subjective perception among healthcare providers of a potential lack of benefit from treatment [42]. In both of these studies, it is unclear what role patient preferences may have played in decisions regarding admission and intensity of care.

Patient and provider decisions regarding care of the critically ill older patient may be based on incomplete or faulty information. In 1995, there were 215,000 deaths attributable to severe sepsis representing 9.3 % of all deaths in the United States and equivalent to the number of deaths attributed to acute myocardial infarction (AMI). The burden of severe sepsis is significant among the older population. The incidence of severe sepsis is 26/1000 among those 85 years and older compared to 5/1000 for adults between that ages of 60 and 64. Moreover, mortality from severe sepsis is 38 % among those ≥85 years of age and <30 % for those between 60 and 64. Despite the increased burden, observational studies of severe sepsis and clinical trials of sepsis therapies often exclude the elderly due to perceptions of increased risk of death or lack of response to treatment. It is important to note that the majority of elderly patients admitted to the ICU with severe sepsis are discharged alive. In addition, as pointed out by Angus et al., with the elderly comprising a substantial proportion of the critically ill population, excluding them from such studies threatens external validity and prevents a comprehensive public policy approach from being created [43, 51].

It is also important to consider the effect of multiple demographic factors on patient outcomes. For example, age and race may be interacting to uniquely affect health outcomes. In a study using data from the National Hospital Discharge Survey, Martin et al. found that African American men presented with the highest rates of sepsis (331 cases/100,000), the youngest age at onset (47 years), and the highest mortality (23 %) [52]. The reasons were not explored, but the authors presented several possible mechanisms including genetic, social, and clinical differences, and called for further investigation to be performed.

Gender

Although women comprise a larger proportion of the US population, the evidence suggests that men have a higher incidence of critical illnesses such as sepsis (mean annual relative risk: 1.3, 95 % CI: 1.2–1.3) [52]. Despite the increased incidence, men do not appear to have a higher case-fatality rate compared to women [25]. In surgical ICUs in the US, for example, men were found to have a higher incidence of sepsis and septic shock compared to women but no difference in hospital or postdischarge mortality [53]. Men are also at risk of prolonged ICU stays compared to women of a similar severity of illness [54]. This may represent differences in end-of-life care, personal preferences regarding care, or other unmeasured factors.

In Europe, some data suggest women have a higher severity of illness and receive a lower overall intensity of care compared to men, but there are no apparent differences in mortality by gender. For example, among 25,998 adults admitted to one of 31 ICUs in Austria, women had higher severity of illness scores (SAPS II 28 vs. 26, $p<0.001$) and in-hospital mortality rates (18 % vs. 17 %, $p=0.04$) compared to men [55]. However, after adjustment for severity of illness, the mortality rate did not differ between men and women. Men received more intensive care compared to women including mechanical ventilation, vasoactive medication, placement of central venous and pulmonary artery catheters, and renal replacement therapy compared to women. These results suggest that the SAPS II score did not fully capture patient severity of illness or other factors besides severity of illness are associated with disparate receipt of intensive therapies between men and women.

Gender differences in receipt of therapies are found in other parts of the world as well. In the U.S., evidence suggests that critically ill men are more likely to receive thrombolytic therapy, emergent surgery, mechanical ventilation, and even coronary artery bypass graft surgery more frequently than critically ill women [56]. Similar results were found in Canada [57]. In a retrospective examination of almost 25,000 critically ill patients admitted to Ontario hospitals over a 2-year period, women were less likely to be admitted into an ICU compared to men (40 % compared to 60 %, $p<0.001$). In fact, older women ($\geq$50 years of age) had 32 % lower odds of being admitted compared to older men. Older women were also less likely to receive mechanical ventilation and pulmonary artery catheterization, and they had shorter ICU stays but longer overall stays in the hospital. Most concerning was the fact that ICU and in-hospital mortality rates were greater for older women compared to older men.

While race, ethnicity, age, and gender all play substantial roles in the development of disparate outcomes, other factors linked to these demographic indices may be equally if not more important. Studies that have explored the root causes of disparities have often found that much of the effect attributed solely to race, ethnicity, gender, or age is significantly attenuated upon consideration of potential confounders. Unfortunately, few studies have incorporated detailed adjustments of these confounding factors into their analyses. A deeper understanding of the effects of these confounding factors is warranted.

Factors Confounding Racial, Ethnic, Age, and Gender Disparities

Genetic Predisposition

Emerging evidence suggests that genetic predisposition may play a role in many disorders affecting the critically ill. However, the extent to which genetic predisposition plays a role in the development of health disparities has not been well described. Perhaps the best evidence linking genetics and premature mortality among the critically ill was from a case–control study of 976 adult Danish nonfamilial decedent adoptees and their biological and adoptive parents [58, 59]. Sørensen et al. found an increased mortality among the biological parents of decedent children but not among their adoptive parents. The associated causes of death included all of the major sources of critical illness: infectious causes (HR: 1.9, 95 % CI: 1.1–3.5), vascular causes (HR: 2.0, 95 % CI: 1.2–3.1), and even natural causes (HR: 1.2, 95 % CI: 1.0–1.4). However, there was no adjustment for demographic or socioeconomic factors. Other studies have identified only a few heritable mutations predisposing to critical illness that are limited mainly to a handful of families. For example, Picard et al. described 3 unrelated children with inherited interleukin-1 receptor-associated kinase (IRAK-4) deficiency rendering them susceptible to recurrent pyogenic bacterial infections [60]. Recent genetic epidemiologic studies have focused on the more prevalent genetic variations [61]. Differing allelic frequencies have been found by both race and gender in patients with ARDS and sepsis. The myosin light chain kinase gene (*MYLK*) encodes a multifunctional protein involved in the inflammatory response [62]. Different single-nucleotide polymorphisms of *MYLK* were found to be associated with sepsis and sepsis-associated ARDS among African Americans and whites. The functional *T-46C* polymorphism in the Duffy antigen/receptor for chemokines (*DARC*) gene is found almost exclusively in persons of African descent and associated with worse clinical outcomes among African Americans with ARDS, perhaps due to an increase in circulating IL-8 [63].

Part of the difficulty in identifying genetic influences on health disparities is due to the wide variability in genetic variants between people of different ancestries. When diverse populations are studied, the associations with a clinical phenotype may be mistaken for being associated with the presence of multiple specific genetic variants determining a predisposing genotype, rather than with an association with prevalence/incidence due to patient ancestry [61]. This spurious association confounding can be overcome by stratifying the case and control groups with different fractions of ancestry from each ancestral subpopulation [64]. Unfortunately, this level of detail is often missing from genetic epidemiology studies in critical illness.

Geographic Residence and Location of Care

Vulnerable critically ill patients are at high risk of experiencing poor health outcomes because of poor access to acute and chronic care, lower socioeconomic status, lower levels of education, higher rates of unemployment, and a higher burden of chronic disease compared to the majority of patients [65]. The imbalances in the geographical distribution of resources, available technological advancements, and distribution of wealth have intentional and unintentional repercussions that have left increasing numbers of the general population unprotected. In the United States, for example, minority populations frequently live clustered together in neighborhoods separated from white populations. Due to the need for emergent care, critically ill patients are often cared for in hospitals nearest to their homes. As a result, critically ill minority patients are more likely to receive care in different hospitals compared to critically ill white patients. The resources available to persons living in minority-predominant neighborhoods are often fewer compared to majority-predominant neighborhoods. This is true in health care as well. Indeed, a recent analysis of Medicare data revealed that only 25 % of hospitals in the United States care for almost 90 % of elderly African American patients [66]. These hospitals tended to be larger and more often were teaching hospitals situated in the southern United States. They also tended to have worse measures of quality of care including treatment of AMI, heart failure, and pneumonia compared to hospitals caring for lower proportions of African American patients.

Hospital level factors may influence health disparities more than patient-level factors. For example, in a study of patients admitted to 28 hospitals for community-acquired pneumonia, African American patients were less likely to receive timely or guideline-adherent antibiotics [67]. Within each hospital, African American and white patients received a similar quality of care. However, among hospitals serving a greater proportion of African American patients, African American and white patients with community-acquired pneumonia were less likely to receive timely antibiotics (OR = 0.8, 95 % CI: 0.8–0.9) and were more likely to receive mechanical ventilation (OR = 1.6, 95 % CI: 1.0–2.4). In a retrospective population-based cohort study including six U.S. states (Florida, Massachusetts, New Jersey, New York, Virginia, and Texas), African Americans had the highest age- and sex-standardized population-based incidence of severe sepsis and hospital-acquired infections and the highest ICU case fatality rates compared to Hispanic and non-Hispanic whites [22]. However, adjustment for clinical characteristics and the treating hospital fully explained the higher case fatality rate.

It appears that when it comes to health care in general in the US, separate may not be equal. For example, risk-adjusted mortality after AMI is higher among African American and white patients admitted to hospitals caring for the highest proportion of African American patients compared to those caring for the lowest [68]. Hospitals with large proportions of African American patients also have worse cardiac arrest outcomes compared to hospitals with predominantly white patients

[69, 70]. This might explain the disparities in survival following cardiac arrest noted between African Americans and whites. Among patients discharged to home following evaluation in emergency rooms in Arizona, Massachusetts, and Utah, African American and Asian patients had lengths of stay ranging from 2 to 14 % shorter than white patients in teaching hospitals, and 1.6 to 16 % longer than white patients in nonteaching hospitals, potentially leading to incomplete clinical evaluations [71]. Finally, in critical care at the end of life, Barnato et al. found differences in ICU use between African Americans, Hispanics, and whites that were attributed to admission into different hospitals with varying ICU utilization patterns at the end of life rather than effects of patient race or ethnicity on ICU use within the hospitals [72]. These studies provide a compelling case to adjust for type and locations of hospitals in all studies of health disparities affecting the critically ill.

The Department of Housing and Urban Development conducted a study that provided insight into successful interventions that may overcome the harmful effects of poverty and segregation on health outcomes [73]. Between 1994 and 1998, 4498 women and children living in public housing in high-priority urban census tracts were randomized to one of three groups. The first group was assigned to receive housing vouchers which could be redeemed only if the participant family moved to a census tract where <10 % of the residents were impoverished and if the participant received counseling regarding moving. Participants in the second group were assigned to receive unrestricted, traditional vouchers with no additional counseling on moving, and participants in the third group served as a control group that received neither vouchers nor counseling. Ten to 15 years later, participants were contacted to determine their body mass index and glycated hemoglobin levels as proxies for the development of high-risk morbid conditions. Participants who had received the vouchers to move to low poverty census tracts combined with counseling on moving were less likely to be obese and had lower glycated hemoglobin levels than participants in the control group. There were no differences in body mass index or glycated hemoglobin among participants in the unrestricted voucher group and participants in the control group. Whether this or similar interventions will have an effect on critical illness outcomes remain to be seen.

Chronic Illness and Access to Care

Comorbid conditions have a significant effect on critical care outcomes [74], and differential prevalence of comorbid conditions as well as differential receipt of treatment of such conditions may explain a significant portion of observed racial and ethnic differences in critical care outcomes. African Americans are more likely to be hospitalized for ambulatory care-sensitive conditions—conditions for which appropriate ambulatory care could prevent hospitalizations—compared to whites [75, 76]. Among patients admitted to ICUs in 35 California hospitals, Erikson et al. found no racial or ethnic differences in in-hospital mortality or ICU length of stay

after adjusting for severity of illness, socioeconomic status, and insurance status [77]. They did find that African American patients were more likely to be admitted with a higher severity of illness and more metabolic derangements suggesting poor access to care and poor control of comorbid conditions prior to admission. The lack of a difference in mortality when compared to white patients could be due to the fact that providing initial care for exacerbations of chronic diseases altered the trajectory of the critical illness. For example, African Americans between the ages of 45 and 64 are 2.5 times more likely to die of heart failure compared to whites of similar age [78]. An African American patient may be admitted to the ICU with an acute exacerbation of previously untreated heart failure with reduced ejection fraction due to poor access to ambulatory care and consequently an inability to initiate routine first-line therapy such as diuretics or ACE inhibitors. With prompt initiation of these agents upon ICU admission, his ICU mortality may improve even though his acute severity of illness on presentation was high, as these agents have previously been demonstrated to be effective in reducing mortality among patients with his degree of CHF. A white patient presenting with a similar CHF exacerbation and an equal acute severity of illness may have an equal or worse mortality as he may have had better access to evidence-based treatments for heart failure while in the ambulatory setting and therefore may already be taking several medications that are indicated for the treatment of CHF. The current measures of ICU severity of illness such as APACHE and SAPS do not account for severity of chronic illness nor do they account for degree of optimization of comorbid conditions. The African American patient may appear sicker according to such severity of illness measures, but require less aggressive treatment from the care team and have a lower ICU mortality. Another explanation for the lack of mortality difference between African American and white patients in this study may be that the participating hospitals were located in the west coast, which care for a higher proportion of white patients and may therefore deliver superior care compared to hospitals in other regions of the country which serve predominantly African American patients.

Uninsurance and Under Insurance

Almost 100 million people worldwide are forced into poverty each year because of catastrophic household medical expenses [79]. As evident in other areas of healthcare, lack of adequate health insurance adversely affects critical care outcomes. For example, low-income and uninsured individuals residing in large metropolitan areas are much less likely to visit with a physician compared to those with higher income or health insurance [80]. Uninsured patients experiencing new serious or morbid symptoms are less likely to receive medical care even though they think they need it [81]. In a systematic review of 29 studies examining the association between insurance status and critical care delivery and outcomes, uninsured patients were less likely to receive critical care services than those who were insured [82]. Following admission, uninsured patients also received fewer procedures compared

to insured patients. Most importantly, lack of insurance was associated with an increased risk of death. In a more recent study not included in the systematic review, Lyon and colleagues performed a retrospective review of patients admitted to Pennsylvania hospitals in 2005 and 2006 [13]. They performed comprehensive patient clinical and demographic adjustments while also considering hospital-level effects and found an increased 30-day mortality among uninsured patients compared to privately insured patients (5.7 % vs. 4.6 %, $p<0.001$). Uninsured patients were also less likely to receive a central venous catheter (7.3 % vs. 9.8 %, $p<0.001$), acute hemodialysis (0.7 % vs. 1.1 %, $p<0.001$), or tracheostomy (8.6 % vs. 22 %, $p<0.001$). As pointed out by the authors, adjusting for hospital-level effects in the analysis allowed comparisons between uninsured and private patients cared for at the same hospitals. Therefore, the lower receipt of critical care procedures and higher mortality rate seen among the uninsured compared to private patients in this study were most likely due to factors occurring within each care setting.

With expansion of insured care under the Affordable Care Act, one might expect greater utilization of critical care services and even a decrease in observed mortality among the critically ill. However, in a comprehensive analysis of Massachusetts data before and after healthcare reform compared to four states that did not enact reform (New York, Washington, Nebraska, and North Carolina), no difference was noted in ICU utilization, discharge destination, or hospital mortality [83]. However, the number of critically ill patients with insurance increased, as was expected. The authors cited several hypotheses for their lack of observed mortality difference, including the unique patient demographics of Massachusetts where only 9 % of patients were uninsured compared to a national average of 17 %. The population of Massachusetts also has a higher baseline socioeconomic status and less racial and ethnic diversity compared to the rest of the nation. Another possibility is that the association between lack of health insurance and mortality observed in prior studies may have been due to other unmeasured factors for which lack of insurance served as a proxy (i.e., poverty). These unmeasured factors may not have changed immediately following insurance expansion. In a study comparing 5 years before Medicaid to have expansion to 5 years after expansion in New York, Maine, and Arizona were found to have a relative reduction in all-cause mortality of 6.1 % or 20 deaths per 100,000 adults compared to neighboring states that did not undergo Medicaid expansion [84]. Mortality reductions were greatest among older adults, nonwhites, and residents of poorer counties.

In 2008, Oregon used a lottery system to select from those individuals waiting for Medicaid expansion. About 2 years after the lottery, 6387 adults who had been selected to apply for Medicaid coverage were compared with 5842 adults who had not been selected [85]. Medicaid coverage was associated with a decreased likelihood of a positive screen for depression (−9 %, 95 % CI: −17 to −1.6 %, $p=0.02$), increased use of many preventive services, and nearly complete elimination of potentially catastrophic out-of-pocket medical expenditures. Among those covered by Medicaid, more cases of diabetes were diagnosed (3.8 % increase, 95 % CI: 1.9–5.7 %) and a higher proportion of patients were using diabetes medications (5.4 % increase, 95 % CI: 1.4–9.5 %). There was no difference in the use of medica-

tions for hypertension or hyperlipidemia, nor was there a difference in average glycated hemoglobin levels. While physical health failed to improve in the first 2 years following expanded Medicaid coverage, there was greater healthcare utilization and reduced financial strain.

Work Trajectory and Unemployment

Work may offer many people a sense of accomplishment and well-being, but for some individuals, work can have deleterious effects on health [86]. Over the last half-century, women have had increased representation in the labor force. Despite this increased representation, African American and white women have had significantly different work trajectories. Black women are more likely to work in jobs with lower earnings, little room for advancement, and high risk of termination [87]. Using data from the National Longitudinal Survey of Mature Women, Shippee et al. found that Black working women who had felt that their work had progressed in the past 10 years had a 24 % lower mortality risk compared to those who felt that their work was static or had regressed. This result persisted despite adjusting for personal demographics, type of occupation, health characteristics, family life, and personal and household wealth. We were unable to find any studies exploring the effects of work trajectory on critical care outcomes.

Income Inequality

Income has a significant effect on health outcomes. Low income is associated with low birth weight, poor educational outcomes, unemployment, work disability, lack of medical insurance, increased medical expenditures, smoking, and sedentary activity [88]. It should come as no surprise, therefore, that income inequality is also associated with differences in all-cause age-adjusted mortality [89]. Across Europe, countries with a lower proportion of their population in relative poverty have higher average life expectancies [90].

Bein et al. prospectively administered a questionnaire that assessed patient socioeconomic status (level of education, occupation, income, marital, and health insurance status) to the surrogates of 1006 patients in a 24-bed surgical ICU of a tertiary hospital in Germany [91]. They found patients of lower socioeconomic status had a higher adjusted odds for ICU length of stay and a lower adjusted odds for visits from friends and family compared to patients with higher socioeconomic status. This result has not been replicated in the United States. In the previously mentioned study involving multiple hospitals in California, Erickson et al. found that socioeconomic status (and higher admission severity of illness) attenuated the increased ICU length of stay identified in African Americans [77]. This demonstrates the importance of including multiple patient level factors in disparities studies.

In spite of the previously mentioned associations between low income and increased mortality, a retrospective study of 38,917 patients admitted to either of two academic medical centers in Boston between 1997 and 2007 found that the percentage of census tract residents below the federal poverty line was not associated with all cause 30-day, 90-day, or 1-year mortality [92]. It was also found to not be associated with 90- and 365-day mortality postcritical care initiation. The study did not include severity of illness information based on physiologic parameters but did include comorbid conditions.

In summary, several factors may confound the relationship between race, ethnicity, age and gender, and health outcomes, including genetic predisposition, geographic location, chronic illness, access to care, and socioeconomic status. Such factors should be adequately addressed in any study of health disparities before valid conclusions can be made.

Critical Care Settings and Conditions Where Health Disparities Have Been Described

Emergency Department

The emergency department remains the primary source of ICU admissions. Despite this, there is a paucity of data regarding emergency department care of the critically ill [93]. To our knowledge, there are no national databases tracking critically ill patients in the emergency department. This leads to an inability to accurately assess the proportion of emergency department patients that are critically ill, the quality of the care that is delivered to them, and how our care delivery in this setting has changed over time.

Even with the lack of national emergency department data on critical illness, important work in health disparities has been performed in the emergency department. A seminal study in health disparities was conducted in an emergency department in Los Angeles in 1993, involving chart review for 139 Hispanic and non-Hispanic white adult patients who presented to the emergency department of a level I trauma center with isolated long-bone fractures [94]. Hispanics remained more likely than non-Hispanic whites to not receive pain medication for their acute fractures after adjustment for several patient and physician characteristics (odds ratio: 7.5, $p<0.01$). A follow-up study in the same setting found that despite Hispanics receiving less analgesia they did not differ from non-Hispanic whites in their delineation of pain and their physicians rated their pain similar to non-Hispanic whites [95]. This suggests that other factors were responsible for lack of an equitable receipt of analgesia among Hispanic patients.

Factors affecting triage of critically ill patients in the emergency department may also influence disparities, and prehospital therapy may influence outcomes in critical illness by affecting appropriate triage. In one study of patients with sepsis, patients that arrived by ambulance had a higher likelihood of receiving immediate

care (including a shorter time to first antibiotics and a shorter time to initiation of early goal directed therapy) compared to "walkins" [96]. For patients who are unable to afford the cost of an ambulance and instead present to their local emergency department by their own means, this can significantly affect their survival. How this further modifies existing racial, ethnic, gender, and age-related disparities is unclear.

Delayed transfer of patients from the ED to the ICU also has a significant impact in outcomes. A study conducted using the Project IMPACT database demonstrated increased ICU and inhospital mortality rates and prolonged hospital lengths of stay following ICU discharge for patients with at least a 6 h delay in ICU transfer from the ED [97]. Unfortunately, few patient level demographics were available to look for associations with health disparities. However, similar findings were demonstrated in a Brazilian study [98]. Such delays are not uncommon and are related to availability of critical care beds in the same institution, the need for interhospital transfer due to need for higher level resources, and physician and nursing staffing in the emergency department and ICU.

Intensive Care Unit

The intensive care unit is the setting for the majority of studies evaluating health disparities among the critically ill. Common conditions encountered in the ICU have received significant attention.

Acute Respiratory Distress Syndrome

In 2012, the definition of ARDS was updated. The new Berlin definition is less ambiguous and has better predictive validity for mortality compared to the previous standard, implemented in 1994 by the American-European Consensus Conference (AECC) [99]. However, the vast majority of ARDS research in general and ARDS health disparities research in particular has relied on the AECC definition. At present, it is unclear what effect the new definition will have on identifying health disparities in ARDS.

Epidemiologic data regarding the incidence and outcomes of ARDS has been hampered by inconsistent definitions, diagnostic misclassification, single-center studies, and limited durations of observation. One of the few studies to overcome these limitations evaluated data from 18 hospitals in King County, Washington as well as 3 hospitals in adjacent counties [100]. The crude incidence of ARDS was 78.9 per 100,000 person-years, and the age-adjusted incidence was 86.2 per 100,000 person-years. In hospital mortality was 38.5 %. The incidence of ARDS varied by age ranging from 16 cases per 100,000 person-years among those between the ages of 15 and 20 years to 306 cases per 100,000 person-years among those between the ages of 75 and 85 years. In-hospital mortality was also found to vary with age, rang-

ing from 24 % among those 15–19 years old to 60 % among those 85 years and older. However, the residents of King County were more affluent, younger, and had a different racial distribution compared to the United States population, and as a result, ARDS incidence and mortality data for minorities and individuals of lower socioeconomic status could not be determined in this study. Using data of patients who participated in the National Heart, Lung, and Blood Institute multicenter, randomized trials of the ARDS Network, Ely and colleagues found similar disparities in mortality among older patients with ARDS. Patients at least 70 years of age had longer times on the mechanical ventilator (median of 19 vs. 10 days, $p<0.001$), longer ICU stays (21 vs. 16 days, $p<0.01$), and a higher risk of in-hospital death (hazard ratio: 2.5, $p<0.001$) [101]. Even after passing spontaneous breathing trials, older patients needed an additional day to obtain unassisted breathing compared to younger patients ($p=0.002$), and 3 additional days before leaving the ICU ($p=0.005$). However, older patients had fewer preexisting comorbid conditions compared to the younger group.

A study using the Multiple Cause Mortality Files from 1979 through 1996 for records containing ICD-9 codes consistent with ARDS found a higher risk of ARDS among women compared to men and African Americans compared to whites [102]. African American men had the highest ARDS-associated mortality compared to white men and men of other minority groups (12.8 per 100,000 individuals per year, compared to 9.1 and 8.6, respectively). African American women similarly had higher ARDS-associated mortality compared to white women and women of other minority groups (7.4 per 100,000 individuals per year, compared to 5.4 and 4.7, respectively). Of particular interest is the fact that a high proportion of African American decedents with ARDS (27 %) were younger than 35 years of age. In contrast, the vast majority of white decedents with ARDS (91 %) were older than 75 years of age. It is unclear whether the higher ARDS-associated mortality rate in African Americans is due to a higher incidence of acute lung injury (ALI) among African Americans or a higher case fatality rate among those with ALI. For example, the excess mortality may have been due to a higher prevalence of comorbid conditions, and the authors were unable to adjust for such confounders in their analysis. Recent work from the ARDS Network found higher 60-day mortality rates among Hispanics (33 %) and blacks (33 %) compared to whites (29 %) [23]. However, after adjustment for gender, receipt of low-tidal volume ventilation, presence of comorbid conditions, cause and severity of ARDS, and severity of acute illness, the association between black race and mortality was no longer significant, but it persisted among Hispanics. The authors found that 30 % of the association between black race and mortality was accounted for in severity of illness. Hispanic ethnicity was not only associated with increased mortality, but also with fewer ventilator-free days. The associations between race/ethnicity and mortality and race/ethnicity and ventilator-free days were not affected by accounting for patient clustering within hospitals. This supports that there were no hospital-specific differences in quality of care as has been suggested in prior studies. An essential consideration that should be made when accounting for ARDS outcomes is that long-term survival in ARDS may not be related to the presence of ARDS, but to the age of the patient, the risk factor for ARDS development, and comorbidity [103].

Given the higher burden of ARDS and severity of illness among minorities and older persons, some have questioned whether such patients are adequately represented in clinical trials. One study compared the rates of enrollment in the ARDS Network studies at the University of California, San Francisco (UCSF) Moffitt-Long University Hospital, which is a large academic medical center, and San Francisco General Hospital, which is the regional safety net hospital [104]. Because both hospitals were part of the same study site, similar screening practices were utilized. A total of 7434 patients were screened and 902 (12 %) were enrolled. The most common reason for not being enrolled was not being medically eligible (45 % at Moffitt-Long compared to 37 % at San Francisco General). Among eligible patients, 89 % of patients at Moffitt-Long were enrolled compared to 29 % as San Francisco General ($p<0.001$). The biggest factor that influenced enrollment among eligible patients at San Francisco General was the lack of available surrogates (40 % of eligible patients compared to only 1 % at Moffitt-Long, $p<0.001$). Patient and family refusal was also higher at San Francisco General (6 % vs. 1 % at UCSF, $p<0.02$). This was particularly common among minority families.

In a larger study that examined enrollment across the ARDS Network studies, Cooke et al. found no differences in the likelihood of enrollment across all racial and ethnic groups [105]. Among excluded patients, minority patients were more likely to be excluded due to patient inability to consent or lack of a surrogate. African American patients were more likely to be excluded compared to white patients as a result of patient or family refusal. Patients over 75 years of age were less likely to be enrolled than younger patients, but older women were more likely to be enrolled than older men. Medical comorbidity had the largest effect on enrollment among older patients. Enrolled patients had lower PAO_2/FIO_2 ratios and were more often cared for in medical compared to surgical ICUs than nonenrolled patients.

Delirium

The reported incidence of delirium among critically ill patients ranges 16–89 % depending on the criteria used for assessment and the populations studied. An important risk factor for the development of delirium in the intensive care unit is receipt of mechanical ventilation [106, 107]. Patients who experience delirium upon admission are more likely to have prolonged hospitalizations. Mortality is higher among patients with delirium compared to patients without delirium (34 % vs. 15 %, HR: 3.2, $p=0.008$) [108]. The risk for delirium increases with increasing age with a prevalence of 14 % among those over age 85 [109]. Among older patients, dementia is a significant risk factor for the development of delirium [110]. Unfortunately, delirium is often missed by both intensivists and ICU nurses due to its overlap with dementia, its fluctuating nature, and infrequent use of validated screening instruments [111]. Little information is available regarding the effects of patient and hospital factors and delirium-related outcomes.

Stroke

Most disparities-related research in the field of neurocritical care has focused on patients with stroke. In 1999, the Centers for Disease Control and Prevention listed decline in deaths from coronary heart disease and stroke as one of the ten greatest public health achievements in the US [112]. However, while the mortality from stroke continues to decline, the mortality among different subgroups with stroke is widening suggesting worsening of health disparities. In 2010, non-Hispanic whites between the ages of 45 and 64 years had a mortality rate from stroke of 16.8 per 100,000 population compared to 18.5 per 100,000 in Hispanics and 46.2 per 100,000 among African Americans of the same age [113]. Hispanics may have a higher stroke incidence, but they have a similar stroke mortality compared to non-Hispanic whites. This may be due to the varied effects of stroke among Hispanic subgroups. For example, Mexicans may have a lower mortality from stroke compared to Puerto Ricans and Cubans [114]. Researchers suggest that observational studies with oversampling of Hispanic participants are needed to better understand these findings.

The mortality rate ratio for stroke has not improved significantly for African Americans compared to whites, and African Americans continue to have a 2–3 times greater prevalence. This widening of the mortality rate is generally attributed to whites having more timely access to intensive stroke-related critical care services compared to African Americans [115]. Another reason is the impact of conditions conferring an increased risk for stroke such as smoking and elevated blood pressure. Using data from the REGARDS study, Howard et al. found that a 10 mmHg increase in systolic blood pressure was associated with an 8 % (95%CI: 10–16 %) increase in stroke risk in whites, but a 24 % (95 % CI: 14–35 %) increase among African Americans [116]. In a Cox proportional hazard model adjusting for gender and use of hypertensive medications, African Americans between the ages of 45 and 64 with systolic blood pressures less than 120 mmHg had a similar risk of death compared to whites of the same age (HR: 0.9, 95 % CI: 0.5–1.6). However, with systolic blood pressure between 140 and 159 mmHg, African Americans had an increased risk of death compared with whites (HR: 2.4, 95 % CI: 1.2–4.7). In the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), African Americans were found to have twice as many small-vessel strokes and strokes of undetermined cause compared to whites [117]. African Americans also had 40 % more large-vessel strokes. The unequal distribution of different types of strokes by race suggests additional factors may be playing a role that have yet to be identified.

Socioeconomic status is also strongly associated with stroke outcomes. In the previously mentioned GCNKSS study, 39 % of the excess risk for stroke among African Americans compared to whites was due to poverty [118]. In the Netherlands, lower education levels were associated with higher disability rates within the 3 years following a stroke and a greater likelihood of requiring institutionalized care [119]. When education and income were combined into a proxy measure for socioeconomic status, low socioeconomic status was associated with increased stroke mortality in men ($p<0.001$) and accounted for 14–46 % of excess stroke risk in

African Americans ($p<0.05$) [120]. Among women, the same relationship between socioeconomic status and mortality was not found.

Despite accounting for over 60 % of patients presenting with stroke, women have a 30 % lower odds of receiving rt-PA treatment compared to men [121]. This gender disparity exists in spite of ample data demonstrating the cost effectiveness of thrombolysis in acute stroke in both men and women [122, 123]. Part of the explanation may be gleaned from a study conducted in 12 hospitals in the Netherlands where women were more likely to present with stroke at an older age and after the allotted 4-h time window for administration [124]. Unfortunately, in the US, the rates of thrombolysis for acute stroke are extremely low for all patients and have been slow to improve (1.4 % in 2001 to 4.5 % in 2009) despite rt-PA being available for use since 1996 [125]. With such abysmal rates of utilization overall, differences by race or gender are difficult to detect.

Regional disparities have been well defined in regards to stroke outcomes. For over four decades, we have noted a significant difference in stroke outcomes of patients residing in the 11 state region extending from Louisiana to Virginia [126]. In fact, the average mortality is 20–25 % higher in this "Stroke Belt" compared to the rest of the nation [115]. The NIH-sponsored Reasons for Geographic and Racial Differences in Stroke (REGARDS) project is a population-based longitudinal cohort study examining the risk factors for stroke among 30,239 African American and white persons over age 45. Participants were recruited from 2003 through 2007 and followed through 2011. African Americans and inhabitants of the "Stroke Belt" were oversampled. A recent finding from that study demonstrated that only 20 % of African American and white stroke participants were evaluated in a Joint Commission-certified primary stroke center. While race and gender were not associated with clinical evaluation at a Joint Commission accredited primary stroke center, both rural residence (OR: 0.39; 95 % CI: 0.22–0.67) and a history of previous stroke (OR: 0.46; 95 % CI: 0.27–0.78) were [127]. A study by the Neurocritical Care Society found the greatest need for neurocritical care units was located in the South, where access is the poorest [128]. This region of the US may also have a higher incidence of cognitive decline suggesting the risk for additional adverse neurologic events may also be prevalent [129]. However, preliminary work has not demonstrated a relationship between residing in a health professional shortage area and use of less cardiovascular disease preventative medications [130].

Trauma

Disparities have been documented for critically ill patients following traumatic injury. Using the National Trauma Data Bank, which is the largest database of trauma inpatients in the United States comprising almost 700 trauma centers and hospitals, Haider et al. found that race and insurance status were associated with mortality [131]. African Americans and Hispanics with insurance had higher mortality rates compared to whites with insurance (OR: 1.2, 95 % CI: 1.1–1.2 and OR: 1.5, 95 % CI: 1.4–1.6). However, uninsured African Americans and Hispanics had

even higher rates compared to whites with insurance (OR: 1.8, 95 % CI: 1.6–1.9 and OR: 2.3, 95 % CI: 2.1–2.5). In a subsequent reevaluation of the National Trauma Data Bank including adjustment for centers caring for a high proportion of minority patients (≥50 %), Haider et al. found that the association between race and mortality was significantly attenuated after accounting for the overall high mortality rates observed in hospitals carrying for predominantly minority trauma patients [132, 133]. As stated previously, consideration of factors confounding the relationship between race, ethnicity, and adverse outcomes must be included in disparities research to derive an accurate understanding of the underlying mechanisms at work.

Following trauma-related ICU stays, African American and Hispanic patients are less likely to be transferred to a rehabilitation service compared with non-Hispanic whites (OR 0.85; 95 % CI 0.8–0.9, $p<0.0001$) [134]. This may be explained by lack of health insurance [135].

In a review of adult trauma patients with a hospital length of stay >72 h in the National Trauma Data Bank, women experienced a 21 % lower adjusted odds of death compared to men [136]. Women were also less likely to experience many of the complications following trauma that men experienced including ARDS, pulmonary embolism, and acute kidney injury. Women did have an increased risk of respiratory tract infections compared to men.

Elderly trauma patients have a greater risk of complications and an increased risk of death compared to younger trauma patients. The mortality risk for trauma increases significantly after age 57 (OR: 5.6, $p=0.04$) compared to the youngest patients [137]. Given this increased risk, elderly patients derive a significant mortality benefit from admission to a trauma center (OR: 0.83, $p=0.04$). In fact, the number needed to transfer to prevent one death decreases as the patient's age increases. Despite this compelling evidence, many elderly patients continue to be improperly triaged to less than ideal settings rather than high-level trauma centers.

Pulmonary Embolism

Pulmonary embolism (PE) represents a significant cause of morbidity and mortality, contributing to at least 100,000 deaths in the United States each year. As the most common preventable cause of mortality during hospitalization, pulmonary embolism is known to be a risk factor for short- and long-term complications with an attributed mortality of 2–6 % in stable patients and up to 30 % in those presenting with hemodynamic instability or shock. In a very large sample (1.3 million) of surgical and nonsurgical patients from the Nationwide Inpatient Sample, the proportion of white patients diagnosed with pulmonary embolism decreased from 83 % in 1998 to 76 % in 2004 while the proportion of African American patients diagnosed with pulmonary embolism increased from 12 % in 1998 to 16 % in 2004. The overall case fatality rate from pulmonary embolism decreased from 12.3 % in 1998 to 8.2 % in 2005 [138]. However, the nationwide the case fatality rate stratified by race was not reported. Heit et al. found racial differences in presentation and risk factors for pulmonary emboli among 2397 patients enrolled from seven centers of the CDC

Thrombosis and Hemostasis Centers Research and Prevention Network between 2003 and 2009 [139]. African American were less likely to present with deep venous thromboses and pulmonary emboli compared to whites (20 % vs. 27 %, p = 0.006). African Americans were also less likely to present with isolated deep venous thromboses without pulmonary emboli compared to whites (52 % vs. 58 %, p = 0.02). However, African Americans were more likely than whites to present with pulmonary emboli without deep venous thromboses (28 % vs. 14 %; $p < 0.0001$). African Americans also had a lower prevalence of identifiable risk factors such as family history, diagnosed thrombophilia, oral contraceptive use, recent trauma, recent surgery, and infection. However, African Americans were more likely to be obese and to have hypertension, diabetes mellitus, HIV, sickle cell anemia, and end-stage renal disease. The authors posit that African Americans may have undiscovered heritable factors that may be conferring an increased risk for pulmonary emboli. Among patients admitted to Pennsylvania hospitals, African American patients had a higher 30-day mortality from pulmonary embolism compared to white patients after adjusting for risks for thromboembolic disease, pulmonary embolism prognosis, hospital bed size, insurance status, and treatment (OR: 1.3, 95 % CI: 1.1–1.6) [140]. It is unclear if the mortality differences were attributable to differences in treatment, pattern of thrombosis, or other unidentified factors.

Challenges to Exploring the Topic of Health Disparities in Critical Illness

Over a decade ago, Judith Kaplan and Trude Bennett challenged us to rethink how we use race and ethnicity in biomedical publications [20]. Yet, many of the concerns that they expressed remain unresolved today (Table 13.2). Race and ethnicity continue to be used as fixed, mutually exclusive categories, ignoring the fact that an increasing number of individuals identify with more than one racial/ethnic group and that racial and ethnic self-identification may change with time. Race and ethnicity also continue to be used as poor substitutes for the true factors that need to be identified including income, insurance status, location where healthcare was delivered, neighborhood of residence, and work trajectory. This not only leads to false declarations, but it prevents the field from moving forward as it implies that such factors and their associated outcomes are not modifiable.

It is time for the field of health disparities in critical illness to quickly leap forward from descriptive to intervention-oriented research. Moreover, future research needs to emphasize the specific mechanisms serving as the basis for health disparities development by including more detailed analyses incorporating patient, provider, and hospital-level factors. Journals can facilitate this change by creating consensus guidelines for the publication of health disparities research. A clearer understanding of the underlying factors at work may facilitate the design of novel interventions that can be rigorously evaluated to determine their effect on reducing health disparities. With the rapid changes to critical care looming on the horizon due to a surging demand for services, we cannot afford to continue to be spectators in this crisis.

References

1. Berthelsen PG, Cronqvist M. The first intensive care unit in the world: Copenhagen 1953. Acta Anaesthesiol Scand. 2003;47(10):1190–5.
2. Reisner-Sénélar L. The birth of intensive care medicine: Björn Ibsen's records. Intensive Care Med. 2011;37(7):1084–6. doi:10.1007/s00134-011-2235-z.
3. Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proc R Soc Med. 1954;47(1):72–4.
4. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. N Engl J Med. 2006;355(1):41–50. doi:10.1056/NEJMsa053993.
5. Treggiari MM, Martin DP, Yanez ND, Caldwell E, Hudson LD, Rubenfeld GD. Effect of intensive care unit organizational model and structure on outcomes in patients with acute lung injury. Am J Respir Crit Care Med. 2007;176(7):685–90. doi:10.1164/rccm.200701-165OC.
6. Cooke CR, Watkins TR, Kahn JM, et al. The effect of an intensive care unit staffing model on tidal volume in patients with acute lung injury. Crit Care. 2008;12(6):134. doi:10.1186/cc7105.
7. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J, Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS). Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? JAMA. 2000;284(21):2762–70.
8. Angus DC, Shorr AF, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. Crit Care Med. 2006;34(4):1016–24. doi:10.1097/01.CCM.0000206105.05626.15.
9. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med. 2010;38(1):65–71. doi:10.1097/CCM.0b013e3181b090d0.
10. Carr BG, Addyson DK, Kahn JM. Variation in critical care beds per capita in the United States: implications for pandemic and disaster planning. JAMA. 2010;303(14):1371–2. doi:10.1001/jama.2010.394.
11. Gabler NB, Ratcliffe SJ, Wagner J, et al. Mortality among patients admitted to strained intensive care units. Am J Respir Crit Care Med. 2013. doi:10.1164/rccm.201304-0622OC.
12. Wagner J, Gabler NB, Ratcliffe SJ, Brown SES, Strom BL, Halpern SD. Outcomes among patients discharged from busy intensive care units. Ann Intern Med. 2013;159(7):447–55. doi:10.7326/0003-4819-159-7-201310010-00004.
13. Lyon SM, Cooke CR, Iwashyna TJ, Ratcliffe SJ, Kahn JM. The effect of insurance status on mortality and procedural use in critically ill patients. Am J Respir Crit Care Med. 2011;184(7):809–15. doi:10.1164/rccm.201101-0089OC.
14. Epstein AM, Ayanian JZ. Racial disparities in medical care. N Engl J Med. 2001;344(19):1471–3.
15. Smedley BD, Stith AY, Nelson ARAR, Institute of Medicine (U.S.). Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, DC: National Academy Press; 2003.
16. Foreman MG, Willsie SK. Health care disparities in critical illness. Clin Chest Med. 2006;27(3):473–86; vii. doi:10.1016/j.ccm.2006.04.007.
17. Soto GJ, Gong MN. Healthcare disparities in critical illness. Crit Care Med. 2013;41(12):2784–93. doi:10.1097/CCM.0b013e3182a84a43.
18. Cooke CR, Kahn JM. Deconstructing racial and ethnic disparities in critical care. Crit Care Med. 2010;38(3):978–80. doi:10.1097/CCM.0b013e3181cc15d3.
19. Osborne NG, Feit MD. The use of race in medical research. JAMA. 1992;267(2):275–9.
20. Kaplan JB, Bennett T. Use of race and ethnicity in biomedical publication. JAMA. 2003;289(20):2709–16. doi:10.1001/jama.289.20.2709.

21. Laws MB, Heckscher RA. Racial and ethnic identification practices in public health data systems in New England. Public Health Rep. 2002;117(1):50–61.
22. Barnato AE, Alexander SL, Linde-Zwirble WT, Angus DC. Racial variation in the incidence, care, and outcomes of severe sepsis: analysis of population, patient, and hospital characteristics. Am J Respir Crit Care Med. 2008;177(3):279–84. doi:10.1164/rccm.200703-480OC.
23. Erickson SE, Shlipak MG, Wheeler AP, et al. Racial and ethnic disparities in mortality from acute lung injury. Crit Care Med. 2009;37(1):1–6. doi:10.1097/CCM.0b013e31819292ea.
24. Mayr FB, Yende S, Linde-Zwirble WT, et al. Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis. JAMA. 2010;303(24):2495–503. doi:10.1001/jama.2010.851.
25. Esper AM, Moss M, Lewis CA, Nisbet R, Mannino DM, Martin GS. The role of infection and comorbidity: factors that influence disparities in sepsis. Crit Care Med. 2006;34(10):2576–82. doi:10.1097/01.CCM.0000239114.50519.0E.
26. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Occurrence and outcomes of sepsis: influence of race. Crit Care Med. 2007;35(3):763–8. doi:10.1097/01.CCM.0000256726.80998.BF.
27. Turner D, Simpson P, Li S-H, Scanlon M, Quasney MW. Racial disparities in pediatric intensive care unit admissions. South Med J. 2011;104(9):640–6. doi:10.1097/SMJ.0b013e3182296e52.
28. Newacheck PW, Stein REK, Bauman L, Hung Y-Y, Research Consortium on Children With Chronic Conditions. Disparities in the prevalence of disability between black and white children. Arch Pediatr Adolesc Med. 2003;157(3):244–8.
29. Newacheck PW, Hung Y-Y, Wright KK. Racial and ethnic disparities in access to care for children with special health care needs. Ambul Pediatr. 2002;2(4):247–54.
30. Newacheck PW, Inkelas M, Kim SE. Health services use and health care expenditures for children with disabilities. Pediatrics. 2004;114(1):79–85. doi:10.1542/peds.114.1.79.
31. Williams JF, Zimmerman JE, Wagner DP, Hawkins M, Knaus WA. African-American and white patients admitted to the intensive care unit: is there a difference in therapy and outcome? Crit Care Med. 1995;23(4):626–36.
32. Rapoport J, Teres D, Steingrub J, Higgins T, McGee W, Lemeshow S. Patient characteristics and ICU organizational factors that influence frequency of pulmonary artery catheterization. JAMA. 2000;283(19):2559–67.
33. Derose KP, Baker DW. Limited English proficiency and Latinos' use of physician services. Med Care Res Rev. 2000;57(1):76–91.
34. Flores G. Language barriers to health care in the United States. N Engl J Med. 2006;355(3):229–31. doi:10.1056/NEJMp058316.
35. DuBard CA, Gizlice Z. Language spoken and differences in health status, access to care, and receipt of preventive services among US Hispanics. Am J Public Health. 2008;98(11):2021–8. doi:10.2105/AJPH.2007.119008.
36. Peterson PN, Shetterly SM, Clarke CL, et al. Health literacy and outcomes among patients with heart failure. JAMA. 2011;305(16):1695–701. doi:10.1001/jama.2011.512.
37. Pham K, Thornton JD, Engelberg RA, Jackson JC, Curtis JR. Alterations during medical interpretation of ICU family conferences that interfere with or enhance communication. Chest. 2008;134(1):109–16. doi:10.1378/chest.07-2852.
38. Thornton JD, Pham K, Engelberg RA, Jackson JC, Curtis JR. Families with limited English proficiency receive less information and support in interpreted intensive care unit family conferences. Crit Care Med. 2009;37(1):89–95. doi:10.1097/CCM.0b013e3181926430.
39. Baker DW, Hayes R, Fortier JP. Interpreter use and satisfaction with interpersonal aspects of care for Spanish-speaking patients. Med Care. 1998;36(10):1461–70.
40. Laws MB, Heckscher R, Mayo SJ, Li W, Wilson IB. A new method for evaluating the quality of medical interpretation. Med Care. 2004;42(1):71–80. doi:10.1097/01.mlr.0000102366.85182.47.
41. Mendu ML, Zager S, Moromizato T, McKane CK, Gibbons FK, Christopher KB. The association between primary language spoken and all-cause mortality in critically ill patients. J Crit Care. 2013;28(6):928–34. doi:10.1016/j.jcrc.2013.07.057.

42. Nguyen Y-L, Angus DC, Boumendil A, Guidet B. The challenge of admitting the very elderly to intensive care. Ann Intensive Care. 2011;1(1):29. doi:10.1186/2110-5820-1-29.
43. Milbrandt EB, Eldadah B, Nayfield S, Hadley E, Angus DC. Toward an integrated research agenda for critical illness in aging. Am J Respir Crit Care Med. 2010;182(8):995–1003. doi:10.1164/rccm.200904-0630CP.
44. Bagshaw SM, Webb SAR, Delaney A, et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care. 2009;13(2):R45. doi:10.1186/cc7768.
45. Fuchs L, Chronaki CE, Park S, et al. ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive Care Med. 2012;38(10):1654–61. doi:10.1007/s00134-012-2629-6.
46. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. J Am Geriatr Soc. 2012;60(6):1070–7. doi:10.1111/j.1532-5415.2012.03989.x.
47. Karlsson S, Ruokonen E, Varpula T, Ala-Kokko TI, Pettilä V, Finnsepsis Study Group. Long-term outcome and quality-adjusted life years after severe sepsis. Crit Care Med. 2009;37(4):1268–74. doi:10.1097/CCM.0b013e31819c13ac.
48. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med. 2010;38(5):1276–83. doi:10.1097/CCM.0b013e3181d8cc1d.
49. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787–94. doi:10.1001/jama.2010.1553.
50. Garrouste-Orgeas M, Boumendil A, Pateron D, et al. Selection of intensive care unit admission criteria for patients aged 80 years and over and compliance of emergency and intensive care unit physicians with the selected criteria: an observational, multicenter, prospective study. Crit Care Med. 2009;37(11):2919–28.
51. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303–10.
52. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546–54. doi:10.1056/NEJMoa022139.
53. Wichmann MW, Inthorn D, Andress HJ, Schildberg FW. Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome. Intensive Care Med. 2000;26(2):167–72.
54. Higgins TL, McGee WT, Steingrub JS, Rapoport J, Lemeshow S, Teres D. Early indicators of prolonged intensive care unit stay: impact of illness severity, physician staffing, and pre-intensive care unit length of stay. Crit Care Med. 2003;31(1):45–51. doi:10.1097/01.CCM.0000038743.29876.3C.
55. Valentin A, Jordan B, Lang T, Hiesmayr M, Metnitz PGH. Gender-related differences in intensive care: a multiple-center cohort study of therapeutic interventions and outcome in critically ill patients. Crit Care Med. 2003;31(7):1901–7. doi:10.1097/01.CCM.0000069347.78151.50.
56. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Crit Care. 2012;16(3):R92. doi:10.1186/cc11355.
57. Fowler RA, Sabur N, Li P, et al. Sex-and age-based differences in the delivery and outcomes of critical care. CMAJ. 2007;177(12):1513–9. doi:10.1503/cmaj.071112.
58. Sørensen TI, Nielsen GG, Andersen PK, Teasdale TW. Genetic and environmental influences on premature death in adult adoptees. N Engl J Med. 1988;318(12):727–32. doi:10.1056/NEJM198803243181202.
59. Petersen L, Nielsen GG, Andersen PK, Sørensen TIA. Case-control study of genetic and environmental influences on premature death of adult adoptees. Genet Epidemiol. 2002;23(2):123–32. doi:10.1002/gepi.1122.
60. Picard C, Puel A, Bonnet M, et al. Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science. 2003;299(5615):2076–9. doi:10.1126/science.1081902.

61. Wurfel MM. Genetic insights into sepsis: what have we learned and how will it help? Curr Pharm Des. 2008;14(19):1900–11.
62. Gao L, Grant A, Halder I, et al. Novel polymorphisms in the myosin light chain kinase gene confer risk for acute lung injury. Am J Respir Cell Mol Biol. 2006;34(4):487–95. doi:10.1165/rcmb.2005-0404OC.
63. Kangelaris KN. The association between a DarcGene polymorphism and clinical outcomes in African American patients with acute lung injury. Chest. 2012;141(5):1160. doi:10.1378/chest.11-1766.
64. Pritchard JK, Rosenberg NA. Use of unlinked genetic markers to detect population stratification in association studies. Am J Hum Genet. 1999;65(1):220–8. doi:10.1086/302449.
65. Landrine H, Corral I. Separate and unequal: residential segregation and black health disparities. Ethn Dis. 2009;19(2):179–84.
66. Jha AK, Orav EJ, Li Z, Epstein AM. Concentration and quality of hospitals that care for elderly black patients. Arch Intern Med. 2007;167(11):1177–82. doi:10.1001/archinte.167.11.1177.
67. Mayr FB, Yende S, D'Angelo G, et al. Do hospitals provide lower quality of care to black patients for pneumonia? Crit Care Med. 2010;38(3):759–65. doi:10.1097/CCM.0b013e3181c8fd58.
68. Skinner J, Chandra A, Staiger D, Lee J, McClellan M. Mortality after acute myocardial infarction in hospitals that disproportionately treat black patients. Circulation. 2005;112(17):2634–41. doi:10.1161/CIRCULATIONAHA.105.543231.
69. Merchant RM, Becker LB, Yang F, Groeneveld PW. Hospital racial composition: a neglected factor in cardiac arrest survival disparities. Am Heart J. 2011;161(4):705–11. doi:10.1016/j.ahj.2011.01.011.
70. Ehlenbach WJ, Barnato AE, Curtis JR, et al. Epidemiologic study of in-hospital cardiopulmonary resuscitation in the elderly. N Engl J Med. 2009;361(1):22–31. doi:10.1056/NEJMoa0810245.
71. Karaca Z, Wong HS. Racial disparity in duration of patient visits to the emergency department: teaching versus non-teaching hospitals. West J Emerg Med. 2013;14(5):529–41. doi:10.5811/westjem.2013.3.12671.
72. Barnato AE, Berhane Z, Weissfeld LA, et al. Racial variation in end-of-life intensive care use: a race or hospital effect? Health Serv Res. 2006;41(6):2219–37. doi:10.1111/j.1475-6773.2006.00598.x.
73. Ludwig J, Sanbonmatsu L, Gennetian L, et al. Neighborhoods, obesity, and diabetes—a randomized social experiment. N Engl J Med. 2011;365(16):1509–19. doi:10.1056/NEJMsa1103216.
74. Esper AM, Martin GS. The impact of comorbid [corrected] conditions on critical illness. Crit Care Med. 2011;39(12):2728–35. doi:10.1097/CCM.0b013e318236f27e.
75. Laditka JN, Laditka SB, Mastanduno MP. Hospital utilization for ambulatory care sensitive conditions: health outcome disparities associated with race and ethnicity. Soc Sci Med. 2003;57(8):1429–41. doi:10.1016/S0277-9536(02)00539-7.
76. O'Neil SS, Lake T, Merrill A, Wilson A, Mann DA, Bartnyska LM. Racial disparities in hospitalizations for ambulatory care-sensitive conditions. Am J Prev Med. 2010;38(4):381–8. doi:10.1016/j.amepre.2009.12.026.
77. Erickson SE, Vasilevskis EE, Kuzniewicz MW, et al. The effect of race and ethnicity on outcomes among patients in the intensive care unit: a comprehensive study involving socioeconomic status and resuscitation preferences. Crit Care Med. 2011;39(3):429–35. doi:10.1097/CCM.0b013e318206b3af.
78. Centers for Disease Control and Prevention (CDC). Mortality from congestive heart failure—United States, 1980-1990. MMWR Morb Mortal Wkly Rep. 1994;43(5):77–81.
79. Commission on Social Determinants of Health. Closing the gap in a generation. Geneva: World Health Organization; 2008. p. 1–256.
80. Andersen RM, Yu H, Wyn R, Davidson PL, Brown ER, Teleki S. Access to medical care for low-income persons: how do communities make a difference? Med Care Res Rev. 2002;59(4):384–411. doi:10.1177/107755802237808.

81. Baker DW, Shapiro MF, Schur CL. Health insurance and access to care for symptomatic conditions. Arch Intern Med. 2000;160(9):1269–74.
82. Fowler RA, Noyahr L-A, Thornton JD, et al. An official American Thoracic Society systematic review: the association between health insurance status and access, care delivery, and outcomes for patients who are critically ill. Am J Respir Crit Care Med. 2010;181(9):1003–11. doi:10.1164/rccm.200902-0281ST.
83. Lyon SM, Wunsch H, Asch DA, Carr BG, Kahn JM, Cooke CR. Use of intensive care services and associated hospital mortality after Massachusetts Healthcare Reform. Crit Care Med. 2014;42(4):763–70. doi:10.1097/CCM.0000000000000044.
84. Sommers BD, Baicker K, Epstein AM. Mortality and access to care among adults after state Medicaid expansions. N Engl J Med. 2012;367(11):1025–34. doi:10.1056/NEJMsa1202099.
85. Baicker K, Taubman SL, Allen HL, et al. The Oregon experiment—effects of Medicaid on clinical outcomes. N Engl J Med. 2013;368(18):1713–22. doi:10.1056/NEJMsa1212321.
86. Kivimäki M, Batty GD, Hamer M, et al. Using additional information on working hours to predict coronary heart disease: a cohort study. Ann Intern Med. 2011;154(7):457–63. doi:10.1059/0003-4819-154-7-201104050-00003.
87. Shippee TP, Rinaldo L, Ferraro KF. Mortality risk among Black and White working women: the role of perceived work trajectories. J Aging Health. 2012;24(1):141–67. doi:10.1177/0898264311422743.
88. Kaplan GA, Pamuk ER, Lynch JW, Cohen RD, Balfour JL. Inequality in income and mortality in the United States: analysis of mortality and potential pathways. BMJ. 1996;312(7037):999–1003. doi:10.1136/bmj.312.7037.999.
89. Lynch JW, Kaplan GA. Understanding how inequality in the distribution of income affects health. J Health Psychol. 1997;2(3):297–314. doi:10.1177/135910539700200303.
90. Wilkinson RG. Income distribution and life expectancy. BMJ. 1992;304(6820):165–8.
91. Bein T, Hackner K, Zou T, et al. Socioeconomic status, severity of disease and level of family members' care in adult surgical intensive care patients: the prospective ECSSTASI study. Intensive Care Med. 2012;38(4):612–9. doi:10.1007/s00134-012-2463-x.
92. Zager S, Mendu ML, Chang D, et al. Neighborhood poverty rate and mortality in patients receiving critical care in the academic medical center setting. Chest. 2011;139(6):1368–79. doi:10.1378/chest.10-2594.
93. Halpern NA. Critical care in the emergency department: it's critical to know what's going on! Crit Care Med. 2013;41(5):1367–8. doi:10.1097/CCM.0b013e318283d161.
94. Todd KH, Samaroo N, Hoffman JR. Ethnicity as a risk factor for inadequate emergency department analgesia. JAMA. 1993;269(12):1537–9.
95. Todd KH, Lee T, Hoffman JR. The effect of ethnicity on physician estimates of pain severity in patients with isolated extremity trauma. JAMA. 1994;271(12):925–8.
96. Studnek JR, Artho MR, Garner CL, Jones AE. The impact of emergency medical services on the ED care of severe sepsis. Am J Emerg Med. 2012;30(1):51–6. doi:10.1016/j.ajem.2010.09.015.
97. Chalfin DB, Trzeciak S, Dellinger RP. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. Crit Care Med. 2007;35(6):1477–83. doi:10.1097/01.CCM.0000266585.74905.5A.
98. Cardoso LTQ, Grion CMC, Matsuo T, et al. Impact of delayed admission to intensive care units on mortality of critically ill patients: a cohort study. Crit Care. 2011;15(1):R28. doi:10.1186/cc9975.
99. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33. doi:10.1001/jama.2012.5669.
100. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–93. doi:10.1056/NEJMoa050333.
101. Ely EW, Wheeler AP, Thompson BT, Ancukiewicz M, Steinberg KP, Bernard GR. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. Ann Intern Med. 2002;136(1):25–36.
102. Moss M, Mannino DM. Race and gender differences in acute respiratory distress syndrome deaths in the United States: an analysis of multiple-cause mortality data (1979-1996). Crit Care Med. 2002;30(8):1679–85.

103. Davidson TA, Rubenfeld GD, Caldwell ES, Hudson LD, Steinberg KP. The effect of acute respiratory distress syndrome on long-term survival. Am J Respir Crit Care Med. 1999;160(6):1838–42. doi:10.1164/ajrccm.160.6.9903058.
104. Glassberg AE, Luce JM, Matthay MA, National Heart Lung and Blood Institute Clinical Trials Network. Reasons for nonenrollment in a clinical trial of acute lung injury. Chest. 2008;134(4):719–23. doi:10.1378/chest.08-0633.
105. Cooke CR, Erickson SE, Watkins TR, Matthay MA, Hudson LD, Rubenfeld GD. Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials. Crit Care Med. 2010;38(6):1450–7. doi:10.1097/CCM.0b013e3181de451b.
106. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10.
107. Thomason JWW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care. 2005;9(4):R375–81. doi:10.1186/cc3729.
108. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62. doi:10.1001/jama.291.14.1753.
109. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354(11):1157–65. doi:10.1056/NEJMra052321.
110. Pisani MA, Murphy TE, van Ness PH, Araujo KLB, Inouye SK. Characteristics associated with delirium in older patients in a medical intensive care unit. Arch Intern Med. 2007;167(15):1629–34. doi:10.1001/archinte.167.15.1629.
111. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35(7):1276–80. doi:10.1007/s00134-009-1466-8.
112. Centers for Disease Control and Prevention (CDC). Ten great public health achievements—United States, 1900-1999. MMWR Morb Mortal Wkly Rep. 1999;48(12):241–3.
113. Centers for Disease Control and Prevention (CDC). Underlying cause of death, 1999-2011 request. Available at: http://wonder.cdc.gov/controller/datarequest/.
114. Gillum RF. Epidemiology of stroke in Hispanic Americans. Stroke. 1995;26(9):1707–12.
115. Howard G. Ancel keys lecture: adventures (and misadventures) in understanding (and reducing) disparities in stroke mortality. Stroke. 2013;44(11):3254–9. doi:10.1161/STROKEAHA.113.002113.
116. Howard G, Lackland DT, Kleindorfer DO, et al. Racial differences in the impact of elevated systolic blood pressure on stroke risk. JAMA Intern Med. 2013;173(1):46–51. doi:10.1001/2013.jamainternmed.857.
117. Schneider AT, Kissela B, Woo D, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. Stroke. 2004;35(7):1552–6. doi:10.1161/01.STR.0000129335.28301.f5.
118. Kleindorfer DO, Lindsell C, Broderick J, et al. Impact of socioeconomic status on stroke incidence: a population-based study. Ann Neurol. 2006;60(4):480–4. doi:10.1002/ana.20974.
119. van den Bos GAM, Smits JPJM, Westert GP, van Straten A. Socioeconomic variations in the course of stroke: unequal health outcomes, equal care? J Epidemiol Community Health. 2002;56(12):943–8.
120. Howard G, Russell GB, Anderson R, et al. Role of social class in excess black stroke mortality. Stroke. 1995;26(10):1759–63.
121. Reeves M, Bhatt A, Jajou P, Brown M, Lisabeth L. Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: a meta-analysis. Stroke. 2009;40(5):1743–9. doi:10.1161/STROKEAHA.108.543181.
122. Boudreau DM, Guzauskas G, Villa KF, Fagan SC, Veenstra DL. A model of cost-effectiveness of tissue plasminogen activator in patient subgroups 3 to 4.5 hours after onset of acute ischemic stroke. Ann Emerg Med. 2013;61(1):46–55. doi:10.1016/j.annemergmed.2012.04.020.

123. Penaloza-Ramos MC, Sheppard JP, Jowett S, et al. Cost-effectiveness of optimizing acute stroke care services for thrombolysis. Stroke. 2014;45:1–22. doi:10.1161/STROKEAHA.113.003216.
124. de Ridder I, Dirks M, Niessen L, Dippel D, PRACTISE Investigators. Unequal access to treatment with intravenous alteplase for women with acute ischemic stroke. Stroke. 2013;44(9):2610–2. doi:10.1161/STROKEAHA.113.002263.
125. Kleindorfer D, de los Rios La Rosa F, Khatri P, Kissela B, Mackey J, Adeoye O. Temporal trends in acute stroke management. Stroke. 2013;44(6 Suppl 1):S129–31. doi:10.1161/STROKEAHA.113.001457.
126. Borhani NO. Changes and geographic distribution of mortality from cerebrovascular disease. Am J Public Health Nations Health. 1965;55:673–81.
127. Mullen MT, Judd S, Howard VJ, et al. Disparities in evaluation at certified primary stroke centers: reasons for geographic and racial differences in stroke. Stroke. 2013;44(7):1930–5. doi:10.1161/STROKEAHA.111.000162.
128. Ward MJ, Shutter LA, Branas CC, Adeoye O, Albright KC, Carr BG. Geographic access to US Neurocritical Care Units registered with the Neurocritical Care Society. Neurocrit Care. 2012;16(2):232–40. doi:10.1007/s12028-011-9644-2.
129. Wadley VG, Unverzagt FW, McGuire LC, et al. Incident cognitive impairment is elevated in the stroke belt: the REGARDS Study. Ann Neurol. 2011;70(2):229–36. doi:10.1002/ana.22432.
130. Brown TM, Parmar G, Durant RW, et al. Health Professional Shortage Areas, insurance status, and cardiovascular disease prevention in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. J Health Care Poor Underserved. 2011;22(4):1179–89. doi:10.1353/hpu.2011.0127.
131. Haider AH, Chang DC, Efron DT, Haut ER, Crandall M, Cornwell EE. Race and insurance status as risk factors for trauma mortality. Arch Surg. 2008;143(10):945–9. doi:10.1001/archsurg.143.10.945.
132. Haider AH, Ong'uti S, Efron DT, et al. Association between hospitals caring for a disproportionately high percentage of minority trauma patients and increased mortality: a nationwide analysis of 434 hospitals. Arch Surg. 2012;147(1):63–70. doi:10.1001/archsurg.2011.254.
133. Haider AH, Hashmi ZG, Zafar SN, et al. Minority trauma patients tend to cluster at trauma centers with worse-than-expected mortality: can this phenomenon help explain racial disparities in trauma outcomes? Ann Surg. 2013;258(4):572–9; discussion 579–81. doi:10.1097/SLA.0b013e3182a50148.
134. Shafi S, la Plata de CM, Diaz-Arrastia R, et al. Ethnic disparities exist in trauma care. J Trauma. 2007;63(5):1138–42. doi:10.1097/TA.0b013e3181568cd4.
135. Heffernan DS, Vera RM, Monaghan SF, et al. Impact of socioethnic factors on outcomes following traumatic brain injury. J Trauma. 2011;70(3):527–34. doi:10.1097/TA.0b013e31820d0ed7.
136. Haider AH, Crompton JG, Oyetunji T, et al. Females have fewer complications and lower mortality following trauma than similarly injured males: a risk adjusted analysis of adults in the National Trauma Data Bank. Surgery. 2009;146(2):308–15. doi:10.1016/j.surg.2009.05.006.
137. Goodmanson NW, Rosengart MR, Barnato AE, Sperry JL, Peitzman AB, Marshall GT. Defining geriatric trauma: when does age make a difference? Surgery. 2012;152(4):668–74; discussion 674–5. doi:10.1016/j.surg.2012.08.017.
138. Park B, Messina L, Dargon P, Huang W, Ciocca R, Anderson FA. Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States: findings from the nationwide inpatient sample. Chest. 2009;136(4):983–90. doi:10.1378/chest.08-2258.
139. Heit JA, Beckman MG, Bockenstedt PL, et al. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. Am J Hematol. 2010;85(7):467–71. doi:10.1002/ajh.21735.
140. Ibrahim SA, Stone RA, Obrosky DS, Sartorius J, Fine MJ, Aujesky D. Racial differences in 30-day mortality for pulmonary embolism. Am J Public Health. 2006;96(12):2161–4. doi:10.2105/AJPH.2005.078618.

Chapter 14
Health Disparities in Sleep-Related Breathing Disorders

Jose S. Loredo

Key Points

- The prevalence of snoring and obstructive sleep apnea increases with age.
- The upper airway resistance syndrome is more commonly diagnosed in younger, thinner women.
- Obstructive sleep apnea is strongly associated with male sex, older age, and obesity.
- Race/ethnicity may matter: obstructive sleep apnea is more prevalent in African Americans than in whites, and African Americans are younger, heavier, and sleepier at diagnosis. However, based on the available literature, the prevalence of obstructive sleep apnea is probably not different between Hispanics and whites, but the prevalence of snoring is higher among Hispanics as compared to non-Hispanic whites.
- Gender matters: during evaluation for sleep-disordered breathing, women complain more of insomnia, fatigue, and depression rather than sleepiness.
- Men are at a higher risk of stroke at every level of obstructive sleep apnea severity compared to women.
- Weight changes and exercise produce a larger beneficial effect in the sleep apnea of men compared to women.
- Obstructive sleep apnea may have greater cognitive impact in Hispanic children than in their white counterparts.
- Physicians may be underdiagnosing or slow to make the diagnosis of obstructive sleep apnea in women and in lean individuals who present with sleep-related complaints.
- Lower CPAP compliance is seen in patients of lower socioeconomic status, in African Americans, and in women.

J.S. Loredo, M.D., M.S., M.P.H. (✉)
Department of Medicine, University of California San Diego School of Medicine,
200 West Arbor Dr., San Diego, CA 92103, USA
e-mail: jloredo@ucsd.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_14

Introduction: The Significance of Sleep

Sleep or a sleep-like state is almost ubiquitous, occurring in animals ranging from fruit flies to humans [1, 2]. However, the purpose of sleep is still a question that has not been fully answered. The need for sleep appears counterintuitive to natural selection; however, it is obvious that sleep has physical and mental restorative properties that are essential for survival and health [3, 4]. Sleep produces a transitory state of cardiovascular relaxation that is thought to be important for cardiovascular health [5, 6]. Sleep has been associated with the ability to learn and memory consolidation [7, 8], and more recently sleep has been associated with the turning on of genes that repair neural tissue [9]. Above all, sleep is the ultimate cure for sleepiness.

Most of what is known about the physiology of sleep has been gained in the last 64 years since the discovery of REM sleep in 1951 [10]. From ancient times, sleep was viewed as a completely passive phenomenon, akin to the brain turning off. In fact, the Bible uses sleep as a metaphor for death [11]. However, far from being an inactive time, sleep is a dynamic state, controlled by elaborate and precise sleep stages that have physiological significance. Sleep systematically progress from light sleep (N1 and N2 sleep) to deep sleep (N3) and REM sleep (R). REM sleep is also known as paradoxical sleep for producing profound somatic atonia while maintaining wake-like brain activity. A good night's sleep is characterized by three major factors: sleep schedule, sleep duration, and sleep quality. Disturbance of any of these factors results in negative health outcomes including excessive daytime somnolence [12], fatigue and mood disorders [13, 14], cognitive impairment [15], metabolic disorders [16], cardiovascular disease [17, 18], and increased susceptibility to other disease [19–21].

Since the description of obstructive sleep apnea (OSA) in 1965 [22], sleep-disordered breathing has emerged as the most common sleep disorder evaluated in the sleep laboratory. And because of its strong association with metabolic disease, cardiovascular disease, and mortality [23–25], the public knowledge about OSA has increased dramatically since the 1990s. Yet, OSA is still unknown to many, and there is growing evidence to suggest significant health disparities with respect to OSA diagnosis and management [26]. This chapter will review the available literature on disparities in obstructive sleep-disordered breathing in the U.S. and highlight important gaps in knowledge that may be the focus of future research.

Physiological Changes during Sleep That Predispose to Sleep-Disordered Breathing

Withdrawal of the wakefulness respiratory drive during the transition from wake to sleep results in transient instability of respiratory control that predisposes the individual to sleep-disordered breathing [27]. In normal individuals, the transition from wake to sleep may result in transient episodes of central sleep apnea and Cheyne–Stokes respiration. In the obese or those who have an anatomically compromised upper airway, snoring and/or OSA may be seen during the transition from wake to

sleep. The sleep fragmentation that results from central or obstructive respiratory events at sleep onset may perpetuate the respiratory control instability and predispose the individual to more protracted sleep-disordered breathing during light sleep [27–29].

Falling asleep also promotes sleep-disordered breathing by unmasking the tendency of peripheral chemoreceptors in some individuals to overreact to a disturbance in PCO_2 levels, often described as high loop gain. High loop gain is an engineering term that describes the propensity of a feedback system to overreact to a disturbance [28, 30]. In situations that result in chronic low PCO_2 levels such as congestive heart failure or sleeping at high altitude, falling asleep results in central apnea due to PCO_2 levels dropping below the apnea threshold. High loop gain will promote overshoot of ventilation as the PCO_2 levels rise during the apnea. The hyperventilation then drives the PCO_2 below the apnea threshold again, resulting in a vicious cycle that promotes the recurrence of central apneas (Fig. 14.1) [31]. This is known as periodic breathing. Loop gain appears to play an important role in the development of OSA in those individuals with a tendency to upper airway collapse [32].

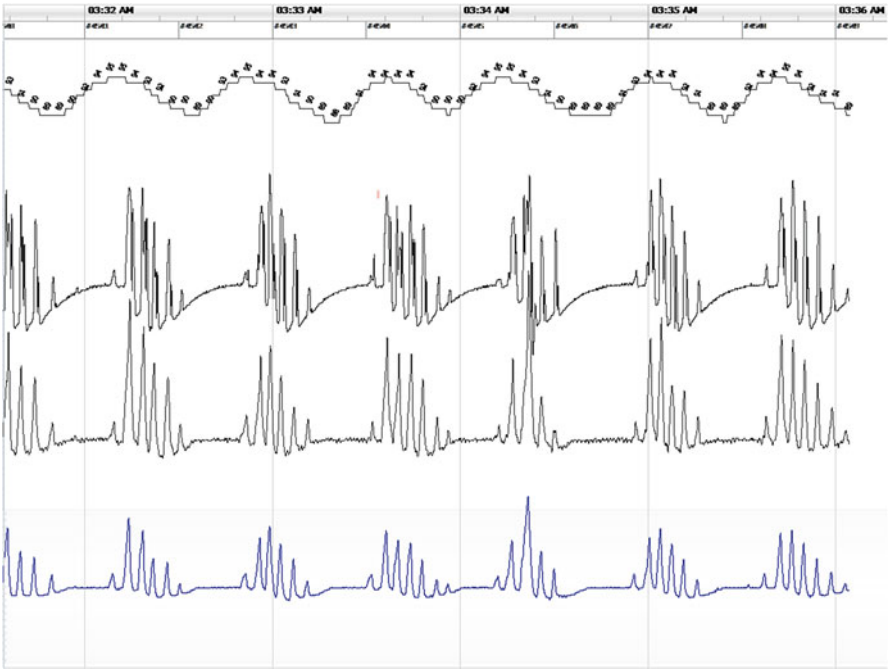

Fig. 14.1 Home sleep recording showing ventilatory response to a disturbance (central apnea) in the setting of high loop gain chemoreceptor response. Notice how high loop gain results in overreaction to the disturbance and promotion of recurrent central apneas. A low loop gain response would result in progressive dampening of the subsequent respiratory event until normal respiration is recovered. From *top* to *bottom*: SpO_2 (channels 1). Nasal airflow (channel 2). Thoracic effort (channel 3). Abdominal effort (channel 4)

Arousals from sleep also promote respiratory instability by producing hyperventilation, which in turn drives the PCO_2 level below the apnea threshold. In the setting of high chemoreceptor sensitivity, this perpetuates respiratory instability and periodic breathing [30].

Normal sleep produces a relative state of hypoventilation, as noted by a 2–3 % reduction in SaO_2 and by a 2–3 mmHg increase in PCO_2 [33]. This degree of hypoventilation has no clinical relevance in normal individuals. However, in persons prone to having low lung volumes due to obesity, respiratory muscle weakness, or in those with intrinsic lung disease, this sleep-related hypoventilation may significantly contribute to central hypopneas and obstructive apneas, especially when sleeping in the supine position [34].

Sleep more than doubles upper airway resistance which can promote sleep-disordered breathing. This is the result of dramatic loss of inspiratory genioglossus motor unit activity at sleep onset resulting in the relaxation of the tongue and pharyngeal dilator muscles, causing a partial collapse of the upper airway [35]. Upper airway resistance is also greatly enhanced by gravity when sleeping in the supine position [36]. This effect can be most marked during the generalized muscle hypotonia of REM sleep. Clinically, it is common for snoring, which is a sign of increased upper airway resistance, to be most severe or present only when sleeping in the spine position.

Importance of Health Disparities in the Practice of Respiratory Sleep Medicine

The importance of sleep in overall health has only recently been recognized [23–25, 37–39]. Sleep-disordered breathing such as snoring and sleep apnea are widespread conditions [37, 40, 41] and are associated with adverse outcomes such as hypertension, diabetes, obesity, myocardial ischemia, stroke, arrhythmia, renal failure, increased healthcare use, and all-cause mortality [23–25]. Most of what is known about the epidemiology and pathophysiology of sleep-disordered breathing has come from research performed in predominantly male non-Hispanic white populations, with limited research in African Americans [37, 42–44]. Therefore, it is difficult to generalize the results to other ethnic minorities or to women. Differences in sleep architecture, duration, and sleep disorders have been reported between various racial groups [44–48]. In a study by Profant et al., African Americans had longer total sleep time, longer REM sleep, and lower deep sleep than whites [44]. In a more recent study from the same laboratory, African Americans had more N2 sleep (light sleep) and less deep sleep than whites, which was associated with a greater personal experience of discrimination as assessed using The Scale of Ethnic Experience [46]. In a review of the literature, children in racial/ethnic and socioeconomic minority groups had a higher prevalence and greater risk for sleep-disordered breathing [48]. This suggests significant environmental or cultural effects on sleep quality and

sleep disorders that may impact the prevalence of cardiovascular disease and affect their evaluation and management [47, 48]. For example, children with health insurance who had OSA were more likely to undergo tonsillectomy to correct the problem than those without health insurance [48]. In 2003, the National Institutes of Health National Sleep Disorders Research Plan (NSDRP) stressed that there were major sleep health disparities in racial and ethnic minorities and in the socioeconomically disadvantaged, who are more likely to sleep in crowded, noisy, or otherwise less than optimal environments [49].

According to data from the 2010 US Census, minority groups in the US are rapidly growing, and by 2043, whites may become the minority. For example, Hispanics or Latinos are now the largest US minority group at 16.3 %; by 2050, it is estimated that Hispanics will make up 29 % of the US population [50]. These great shifts in demographics further stress the need to better understand health disparities and develop policies to help eliminate them.

Sleep-Disordered Breathing

Sleep-disordered breathing can be divided into obstructive (Fig. 14.2), central (Fig. 14.3), and mixed apneas (Fig. 14.4) and hypopneas. Apneas are characterized by complete or nearly complete cessation of airflow for at least 10 s in the adult and for two or more respiratory cycles in the child. Hypopneas are characterized by a 30 % to <90 % decrement in airflow for at least 10 s associated with oxyhemoglobin desaturation of ≥4 %. Alternatively, hypopneas can also be defined as a reduction in airflow of ≥50 % associated with an oxygen desaturation of ≥3 % and/or an arousal from sleep (Fig. 14.5) [51]. The severity of sleep apnea is characterized using the apnea–hypopnea index (AHI), which describes the number of these events per hour of sleep.

Obstructive sleep-disordered breathing is by far the most common of all the three forms. Obstructive events are characterized by complete or partial collapse of the upper airway and persistent respiratory efforts usually in a crescendo pattern terminated by an arousal (Fig. 14.2). Snoring is a sign of partial obstruction and occurs during hypopneas or after termination of an apnea (Fig. 14.5), but it is typically absent during an apnea due to complete obstruction of the upper airway. Snoring is also a prominent feature of the upper airway resistance syndrome (UARS). This is a variant of sleep-disordered breathing that has no apneas, hypopneas, or desaturations. The UARS is characterized by episodes of crescendo snoring and increasingly more negative esophageal and pharyngeal pressure due to crescendo respiratory effort that terminate in an arousal (Fig. 14.6) [52]. These episodes are also known as respiratory effort-related arousals. Clinically, the UARS will present with similar symptoms as OSA [53–55].

Central apneas and hypopneas are the consequence of the cessation or partial reduction of the central respiratory drive, thereby resulting in the absence or reduction of respiratory efforts. Typically, snoring is absent, but gasping and some snoring

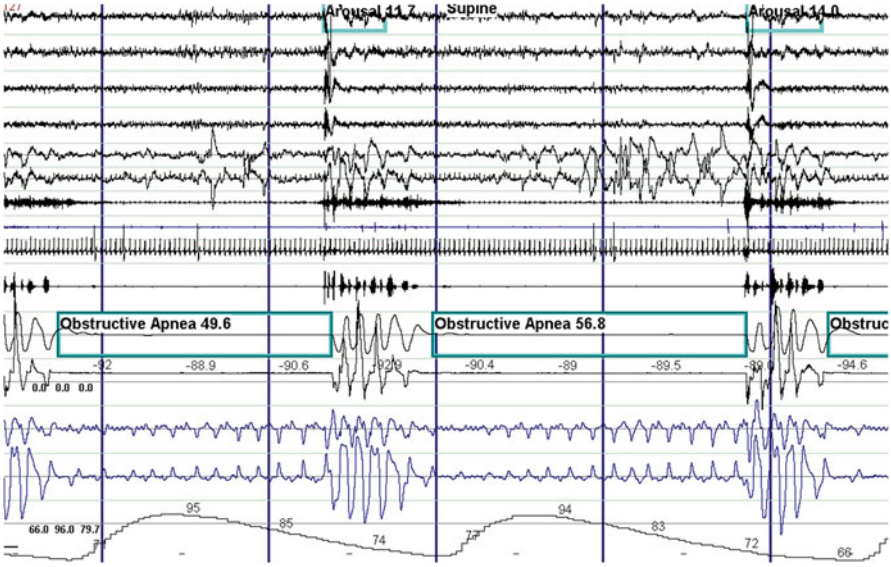

Fig. 14.2 Polysomnographic example of obstructive sleep apnea. These events are characterized by complete obstruction of the upper airway resulting in the absence of airflow while respiratory efforts persist. Gasping for air and snoring is seen when the airway opens during a resulting arousal from sleep. Oxygen desaturation can be severe as in this case. From *top* to *bottom*: EEG channels 1–4. EOG channels 5–6. Chin EMG channel 7. Tibialis anterior EMG channel 8. ECG channel 9. Snoring microphone channel 10. Thermistor and pressure transducer airflow channels 11–12. Chest and abdominal respiratory effort channels 13–14. Oxygen saturation channel 15

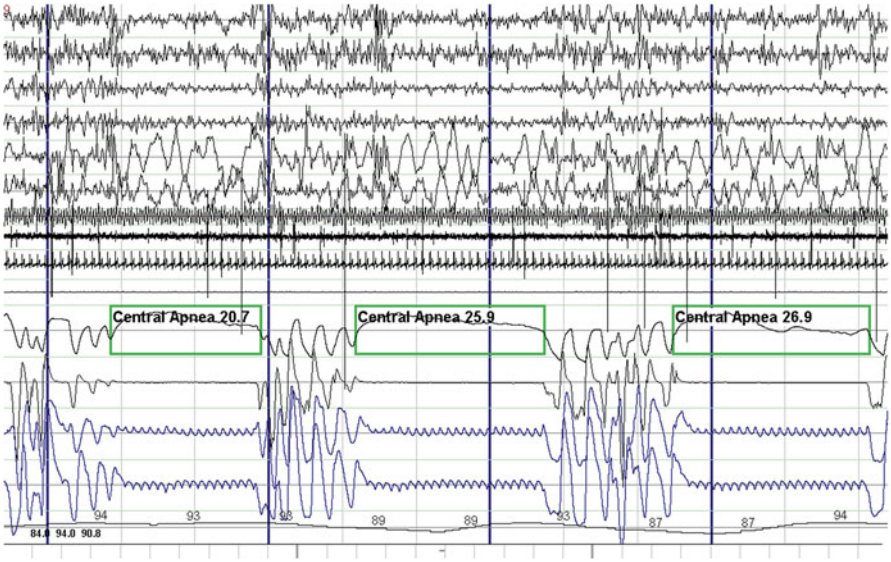

Fig. 14.3 Polysomnographic example of central sleep apnea. These events are characterized by complete cessation of airflow due to lack of respiratory efforts. Waves forms noted in the respiratory effort channels are due to sensor detecting heart pulsations. From *top* to *bottom*: EEG channels 1–4. EOG channels 5–6. Chin EMG channel 7. Tibialis anterior EMG channel 8. ECG channel 9. Snoring microphone channel 10. Thermistor and pressure transducer airflow channels 11–12. Chest and abdominal respiratory effort channels 13–14. Oxygen saturation channel 15

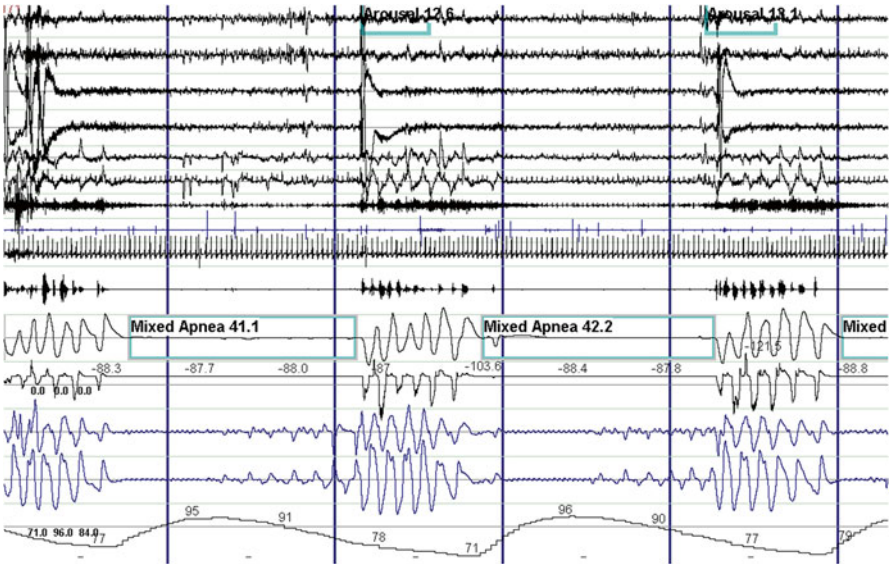

Fig. 14.4 Polysomnographic example of mixed sleep apnea. These events are characterized by complete cessation of airflow and respiratory effort in the first half of the event (central component). Then respiratory efforts start with persistent lack of airflow (obstructive component) in the second half of the event. From *top* to *bottom*: EEG channels 1–4. EOG channels 5–6. Chin EMG channel 7. Tibialis anterior EMG channel 8. ECG channel 9. Snoring microphone channel 10. Thermistor and pressure transducer airflow channels 11–12. Chest and abdominal respiratory effort channels 13–14. Oxygen saturation channel 15

sounds may be heard when respiratory efforts resume after a central apnea or during hyperventilation at the end of a central hypopnea (Fig. 14.3).

Mixed sleep-disordered breathing events have features of both central and obstructive events (Fig. 14.4). Clinically, pure mixed sleep apnea is rare. Mixed apneas and hypopneas generally appear as part of either central or OSA. The type of sleep apnea is determined by the predominant type of event in an individual (i.e., whether more than 50 % of the events are obstructive or central). During such designation, mixed apnea or hypopneas are usually counted as obstructive events since they will respond to CPAP therapy, unlike central sleep apnea.

Except in a few clinical situations, central sleep apnea and Cheyne–Stokes respiration (also known as "periodic breathing" for its waxing and waning airflow pattern (Fig. 14.7)) do not generally occur in the absence of other sleep disorders. Both can be seen transiently during the transition from wake to sleep and in the setting of sleeping at high altitude [30], but these presentations are rarely considered clinically relevant. Central sleep apnea and Cheyne–Stokes respiration disorders can also be seen in the setting of congestive heart failure, use of narcotic pain medications, obesity hypoventilation syndrome, severe central nervous system disease, and idiopathic central sleep apnea [30].

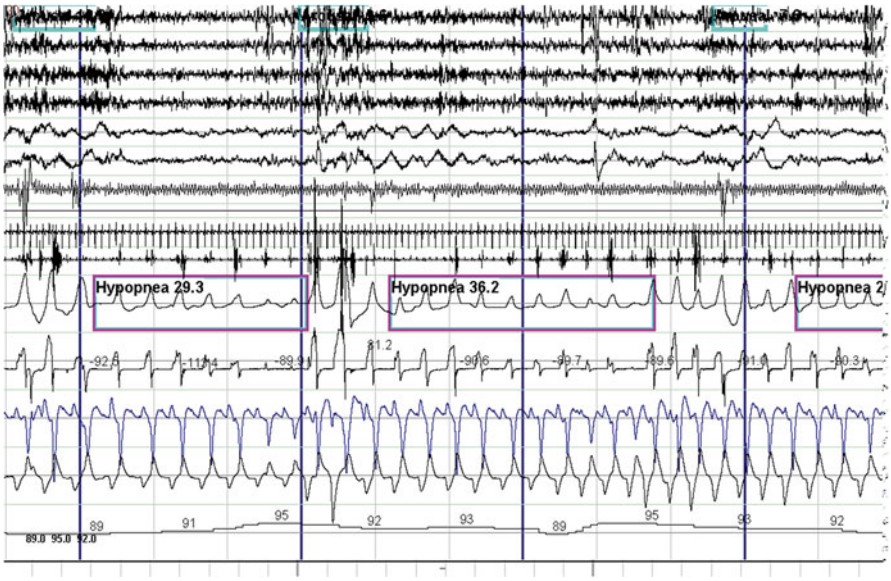

Fig. 14.5 Polysomnographic example of obstructive hypopneas. These events are characterized by partial reduction of airflow. Notice the crescendo snoring during the hypopnea with paradoxical chest and abdominal respiratory movements consistent with partial upper airway obstruction that terminates in an arousal and oxygen desaturation. From *top* to *bottom*: EEG channels 1–4. EOG channels 5–6. Chin EMG channel 7. Tibialis anterior EMG channel 8. ECG channel 9. Snoring microphone channel 10. Thermistor and pressure transducer airflow channels 11–12. Chest and abdominal respiratory effort channels 13–14. Oxygen saturation channel 15

The immediate clinical consequence of central and obstructive sleep-disordered breathing is sleep fragmentation that results in excessive daytime somnolence. Long-term complications of untreated obstructive sleep-disordered breathing syndromes include hypertension, cardiovascular disease, fatigue, depressive mood disorders, and insomnia [24, 25, 56, 57]. In addition, the untreated patient with OSA often complains of a number of psychosocial problems including reduced vigilance, excessive daytime sleepiness, reduced concentration, and deficits of memory and executive function [58], which can result in an increased rate of accidents [59].

Disparities in Obstructive Sleep-Related Breathing Disorders

Snoring

In the 1980s, the self-reported prevalence of snoring was evaluated in a 1222 adult Hispanics living in New Mexico. The prevalence of snoring was greater in men (27.8 %) than in women (15.3 %) and increased with age and obesity for both

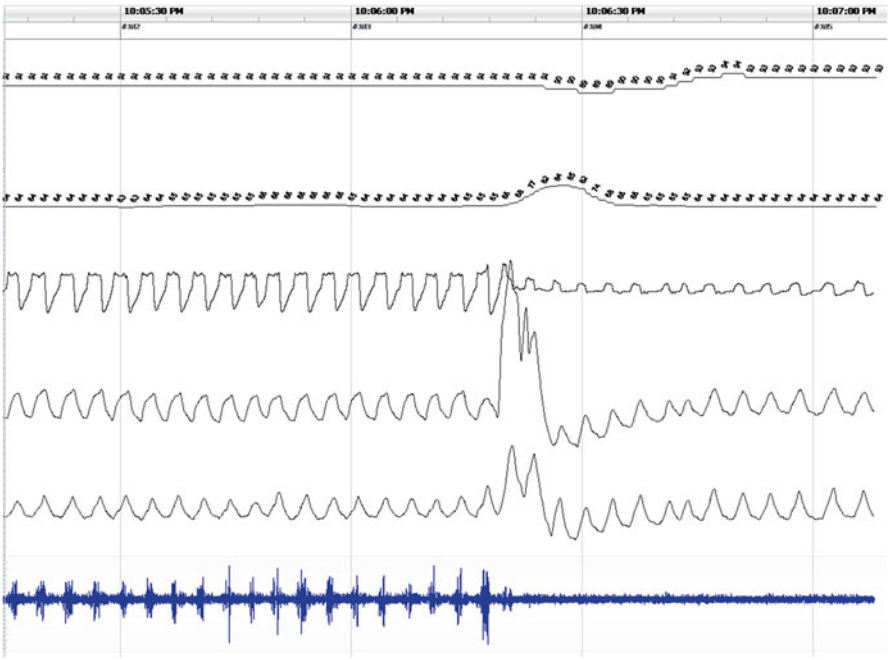

Fig. 14.6 Example of the upper airway resistance during home sleep recording. From *top* to *bottom*: SpO_2 (channels 1). Heart rate (channel 2). Nasal airflow (channel 3). Thoracic effort (channel 4). Abdominal effort (channel 5). Snoring microphone (channel 6). Notice the airflow limitation or flattening on channel 3 associated with snoring (channel 6) and a minor oxyhemoglobin desaturation of <3 % (channel 1) that resolve after an arousal as measured by a transient rise in heart rate (channel 2)

groups, but the prevalence of snoring leveled off after age 59 for men and women. In this study, snoring was associated with myocardial infarction (odds ratio 1.8; 95 % CI 0.9, 3.6) but not with hypertension after controlling for age, gender, obesity, and smoking. Snorers were also sleepier than nonsnorers, suggesting that snorers may have had a higher prevalence of OSA, which was not directly evaluated in this study [60].

The prevalence of snoring has been evaluated in representative samples from the general US population. In the 2005–2006 National Health and Nutrition Examination Survey, the prevalence of snoring was high at 48 % among 6139 individuals older than 16 years [61]. Results from the National Sleep Foundation Sleep in America 2005 poll of 1506 adults (mean age of 49 years, 51.6 % women) showed that the prevalence of snoring was 59 % and habitual nightly snoring was 40 %. Habitual snoring was more common in men [62]. In the 2007–2008 National Health and Nutrition Examination Survey, sleep symptoms were evaluated by race/ethnicity and socioeconomic position in 4081 non-Hispanic whites, African Americans, Mexican Americans, other-Hispanics/Latinos, and Asians. Non-Hispanic whites

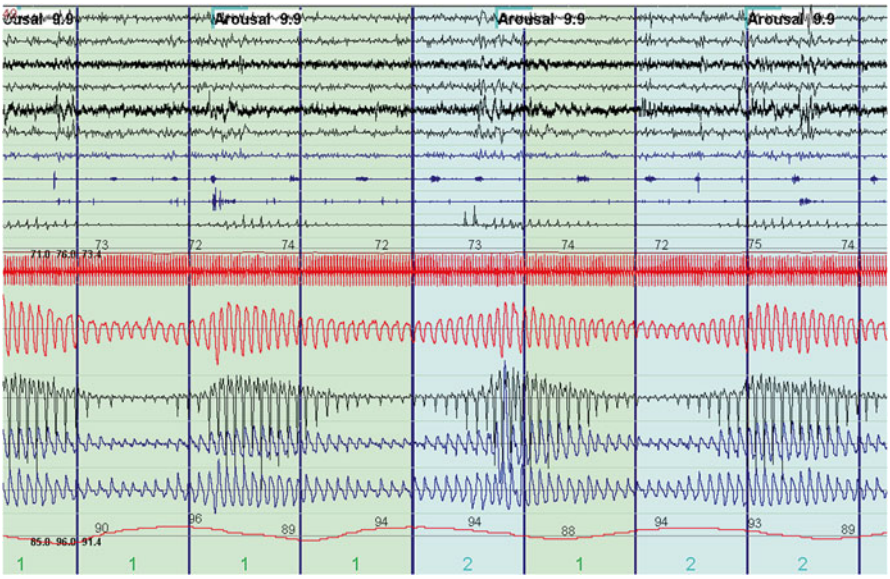

Fig. 14.7 Polysomnogram depicting Cheyne–Stokes ventilation. Notice the waxing and waning airflow pattern (Channels 13–14 from the *top*). Snoring is absent during the hypopnea but can be seen during the hyperventilation portion of the event (Channel 10). Cheyne–Stokes can result in sleep fragmentation as noted by arousals from sleep (EES channels 1–4) and transient desaturations (Channel 16) that predisposes to periodic breathing through high loop gain physiology

represented 72.81 % of the sample, followed by African Americans at 10.29 % and Mexican Americans at 7.55 %. Snoring was more common among males (odds ratio 1.93, 95 % CI 1.66–2.24), other-Hispanics/Latinos (odds ratio 1.37, 95 % CI 1.03–1.83), and those with less than a college education. In this study, African Americans reported more nonrestorative sleep (odds ratio 1.59, 95 % CI 1.25, 2.01) [63].

The Sleep Heart Health Study (1995–2006) is the largest prospective cohort study to assess sleep-disordered breathing and OSA as risk factors for major cardiovascular events, including myocardial infarction and stroke [64]. It evaluated the variations in symptoms of sleep-disordered breathing in 13,194 men and women 40 years of age and older in five major racial/ethnic groups. Snoring was more frequently reported by Hispanic men (odds ratio 2.30, 95 % CI 1.43, 3.69), Hispanic women (odds ratio 2.25, 95 % CI 1.48, 3.42), and Black women (odds ratio 1.55, 95 % CI 1.13, 2.13), compared with the white, American Indian, and Asian Pacific Islander counterparts after adjusting for age, presence of a bed partner, and body mass index [65]. The overall prevalence of self-reported snoring in whites, Hispanics, and African Americans participating in the Sleep Heart Health Study was 34 %. However, the prevalence of self-reported snoring was higher in Hispanics (41 %) compared to whites (34 %), and African Americans (30 %) ($p < 0.05$) [66].

The Northern Manhattan Study examined a cohort of 1605 older adults (mean age 65 ± 8 years) that included predominantly Hispanics (61 %) but also whites

(20 %) and African Americans (19 %). The investigators found the overall prevalence of self-reported habitual snoring was 29 %, but it was much higher in Hispanics (84 %) compared to both African Americans (9 %) and whites (7 %) [67]. In a related study focused on the more elderly participants (mean age 75 ± 9 years, 37 % men), Hispanics more frequently reported habitual snoring (odds ratio 2.8, 95 % CI 1.7–4.5) compared to African Americans and whites. They were also more likely to report long sleep (≥9 h, odds ratio 1.8, 95 % CI 1.1–3.1). There were no differences in sleep complaints between African Americans and whites [68].

The Tucson Children's Assessment of Sleep Apnea study (TuCASA) examined 1494 questionnaires for children 4–11 years old living in Tucson, Arizona. Parents of male Hispanic children were more likely to report that their boys snore frequently (11.4 % vs. 7.4 %, respectively; $p < 0.02$) and were more likely to report excessive daytime sleepiness (9.6 % vs. 5.8 %, respectively; $p < 0.01$) than their white counterparts. There was no difference between Hispanic or white girls with regard to snoring or excessive daytime sleepiness [69]. In children of age 2–6 years attending well-child care visits, the overall prevalence of reported snoring was 13.9 % (95 % CI 10.2, 17.5). However, snoring was found in 18.7 % (95 % CI 13.2, 25.7) of African American children ($n = 150$), 17.5 % (95 % CI 8.6, 32.4) of Hispanic children ($n = 40$), and 8.3 % (95 % CI 4.7, 14.4) of white children ($n = 132$) ($p = 0.031$). The odds ratio of snoring was 2.5 (95 % CI 1.2, 5.5) for African American children and 2.3 (95 % CI 0.8, 6.4) for Hispanic children as compared to their white counterparts [70].

In summary, it appears that the prevalence of habitual snoring in the general adult US population is high, ranging from 27 to 48 %, and as high as 84 % in the elderly, with the higher estimates coming from studies in more recent years [60–62, 67]. Snoring in general is more prevalent in men than in women and increases with age, but its prevalence plateaus after age 59 [60, 62, 63]. In all the studies that have evaluated snoring and ethnicity, the findings are consistent, showing that habitual snoring is more prevalent in Hispanic men and women, in African American women [63, 65–68], and in Hispanic male children [69] and African American children [70] as compared to their white counterparts.

These studies are limited by the self-reported nature of the snoring data, which can hide significant biases. These studies also do not explain why men, Hispanics, and African Americans snore more frequently than other population groups. Clearly more investigation is needed as to the epidemiology of snoring in the US population.

Upper Airway Resistance Syndrome

The diagnosis of the upper airway resistance syndrome (UARS) is difficult to make using the standard polysomnographic montage, especially when a thermistor is used to measure airflow. Guilleminault used an esophageal manometer to confirm the increasingly negative intrathoracic pressure resulting in an arousal, and this technique is currently the gold standard to make the diagnosis of UARS [53, 54]. Others

have used a combination of crescendo snoring associated with increased respiratory effort in the setting of sleep fragmentation to make the diagnosis of UARS [71]. With the advent of the nasal cannula pressure transducers to measure airflow, inspiratory airflow limitation can be determined and used as a measure of increased upper airway resistance to aid in UARS diagnosis [72, 73]. However, noninvasive methods for determining UARS are not yet well validated [54, 74]. The lack of diagnostic consensus has hampered research of UARS in the general population.

In clinical practice, UARS is rarely seen in isolation from OSA [75]. There are very few studies that have addressed the epidemiology of UARS, and all have focused on very specific populations. Kristo et al. reported on 527 patients who underwent evaluation for excessive somnolence in a US military sleep disorders center in 2000 using esophageal manometry during polysomnography. OSA was diagnosed in 72.6 % of these patients as compared to 8.4 % who were found to have pure UARS [76]. In a population of 41 morbidly obese patients (mean BMI 47 kg/m^2, 83 % women) referred for bariatric surgery, the prevalence of UARS based on polysomnographic criteria was 17 % as compared to 71 % who were diagnosed with OSA [71].

Stoohs et al. performed a retrospective evaluation of the characteristics of 2753 patients with sleep-disordered breathing seen in two sleep clinics in Germany from 1996 to 2006. They compared patients with primary snoring ($n=157$), UARS ($n=424$), OSA without sleepiness ($n=562$), and OSA with sleepiness ($n=1610$). Patients with UARS were significantly younger (45.3 ± 12.3 years) than those with primary snoring (48.7 ± 11.8 years), OSA without sleepiness (53.0 ± 12.3 years), and OSA with sleepiness (OSAS) (51.5 ± 11.7 years) ($p<0.02$). Patients with primary snoring and UARS had a lower body mass index than those with OSA and OSAS ($p<0.001$). Also of note, patients with UARS were more likely to be women [77]. No data currently exist examining racial/ethnic or socioeconomic disparities in UARS prevalence.

In summary, the prevalence of UARS in the general population is not known. The current estimates range from 8.4 to 17 % [74, 76], but these figures are based on small research populations with widely different demographic characteristics. However, those with UARS tend to be younger, less overweight, and more frequently female than patients with OSA [71, 77].

The UARS literature is limited by the retrospective nature of the available evidence, the dearth of research in the epidemiology of UARS, the differences in diagnostic methodology used in various studies, and the lack of consensus on UARS as an independent syndrome. Also, the literature has not adequately addressed risk factors related to the prevalence of UARS. Clearly more research is needed to better understand UARS with respect to its epidemiology and potential health disparities.

Obstructive Sleep Apnea

Among all sleep-related breathing disorders, OSA has been the most extensively studied due to its high prevalence and clinical relevance to cardiovascular disease [78]. Epidemiological studies and experimental work in animals support the

assertion that OSA, if left untreated, results in activation of the sympathetic nervous system and eventually systemic hypertension [79–81]. Untreated OSA is also strongly associated with other disease states, including coronary artery disease, congestive heart failure and stroke [78, 82], nocturnal arrhythmias [83], diabetes type 2 [84, 85], obesity [86], inflammation [87], hypercogulable state [88], the metabolic syndrome [89], and increased mortality [90]. Since its initial polysomnographic description in 1965 [22], the prevalence of OSA in the US has been increasing in close association with the obesity epidemic [86, 91].

In 1993, Young and colleagues first reported the prevalence of OSA in a random sample of 602 men and women recruited from the general working population ages 30–60 years (Wisconsin Cohort). Based on an AHI ≥ 5/h, the overall prevalence of OSA was 21.3 %. The prevalence of OSA was 24 % for men and 9 % for women. The prevalence of OSA syndrome (OSA plus Epworth Sleepiness Scale score [ESS] > 10) was 4 % for men and 2 % for women [37]. Since then, the prevalence of OSA has been consistently reported as 2:1 to 3:1 male predominance in the premenopausal years and a nearly 1:1 ratio after menopause [92–94]. Peppard et al. reevaluated the Wisconsin Cohort sample from 1988 to 1994 and 2007 to 2010 and adjusted for age, sex, and BMI using sampling weights provided by the respective US National Health and Nutrition Examination Survey (NHANES) for subjects 30–70 years old. The sample consisted of 1520 study participants (96 % non-Hispanic white) who were assessed for sleep-disordered breathing between 1988 and 2011. Women made up 45 % of the sample. They estimated an overall prevalence of OSA (AHI ≥ 5/h) 20 years later at 26 % (95 % CI 24,28). The overall prevalence of OSA syndrome (AHI ≥ 5/h and ESS >10) was not reported. However, the prevalence of OSA (Table 14.1) and OSA syndrome (Table 14.2) was greater for men and women in 2007–2010 as compared to 1988–1994 [91].

Aging is a major risk factor for the development of OSA and increased prevalence of OSA is found in men and women with increasing age. Ancoli-Israel and colleagues reported that 62 % of community-dwelling older adults (>65 years of age) had significant OSA (AHI ≥ 10/h) based on unattended cardiorespiratory home sleep recordings [95]. The Sleep Heart Health Study also showed the average prevalence of OSA (AHI ≥ 15/h) increased stepwise until approximately age 60, after which it leveled off at a prevalence of about 20 % in a community-dwelling popula-

Table 14.1 Wisconsin Cohort study

	1988–1994 data		2007–2013 data	
Gender	%	95 % CI	%	95 % CI
Men	26.4	23.9, 28.9	33.9	30.8, 37.0
Women	13.2	11.4, 15.3	17.4	15.2, 20.0

Prevalence estimates of obstructive sleep apnea (AHI ≥ 5/h) adjusted for age, gender, and BMI using weights provided by the NHANES for men and women ages 30–70 years. Reprinted with permission from Oxford University Press [91]

AHI apnea hypopnea index, *NHANES* US National Health and Nutrition Examination Survey, *BMI* body mass index, *CI* confidence interval

Table 14.2 Wisconsin Cohort study

	1988–1994 data		2007–2013 data	
Gender	%	95 % CI	%	95 % CI
Men	10.8	9.0, 12.6	14.3	12.0, 16.4
Women	3.8	2.9, 4.9	5.0	3.9, 6.3

Comparison of prevalence estimates of obstructive sleep apnea syndrome (AHI ≥ 5/h, ESS score > 10) adjusted for age, gender, and BMI using weights provided by the NHANES for men and women ages 30–70 years. Reprinted with permission from Oxford University Press [91]
AHI apnea hypopnea index, *NHANES* US National Health and Nutrition Examination Survey, *BMI* body mass index, *CI* confidence interval, *ESS* Epworth Sleepiness Scale

tion of 5615 men and women ages 40–98 years [92]. This is very similar to the plateau effect after age 59 seen in the prevalence of snoring described by Schmidt-Nowara et al. [60].

Comparison of the prevalence of OSA by race or ethnicity has been directly evaluated only in a few studies. In the 1990s, Kripke et al. performed overnight oximetry in 190 women and 165 men (age 40–64 years) in southern California, where there is a high proportion of Hispanics of Mexican descent. Based on these data, the authors estimated that 16.3 % of Hispanics had ≥20 episodes of transient oxyhemoglobin desaturation (≥4 %) per hour of sleep, akin to having moderate OSA, compared to only 4.9 % of non-Hispanic Whites [96]. The Hispanic Community Health Study/Study of Latinos (2008–2013) is a multicenter community-based cohort study that evaluated the prevalence of risk factors for sleep disorders and as well as for heart, lung, blood, kidney, liver, endocrine, and cognitive disorders [97]. This study performed unattended home sleep recordings and recently reported the prevalence of OSA for 14,400 participants. The age-adjusted prevalence of OSA for AHI ≥ 5/h, ≥15/h, and ≥30/h was 25.8 %, 9.8 %, and 3.9 %, respectively [41]. Consistent with prior studies, OSA was associated with male sex, obesity, and older age and the prevalence for OSA (AHI ≥ 5/h) was similar to the most recent prevalence estimates in whites [91]. Ancoli-Israel et al. evaluated the prevalence of OSA in elderly African Americans ($n = 54$) and whites ($n = 346$) older than 65 years of age. African-Americans had significantly greater AHI than whites (72.1/h vs. 43.3/h; $p = 0.014$), and there were more African Americans (17 %) with severe OSA (AHI ≥ 30/h) than whites (8 %) ($p = 0.034$; relative risk = 2.13; 95 % CI 15–19 %). This association remained significant after controlling for age, gender, and body mass index [98]. Redline et al. evaluated 225 African Americans and 622 whites using a cardiorespiratory home sleep recordings and reported that African Americans ≤25 years old had higher AHI and higher prevalence of increased apneic activity (odds ratio 1.88, 95 % CI 1.03–3.52) after adjusting for obesity, sex, proband sampling, and familial clustering. The authors concluded that young African Americans may be at increased risk for sleep apnea [99]. There are no studies directly comparing the prevalence of OSA between Asians and whites. However, in middle-aged Asian men and women the prevalence of symptomatic OSA diagnosed by polysomnography (AHI ≥ 5/h plus ESS >10) has been reported as similar to that in whites (4.1–7.5 % for men and 2.1–3.2 % for women) [37, 100–103].

In summary, OSA is strongly associated with male gender [37, 92–94], obesity [86], and increasing age [92, 96], but there appears to be a plateau effect on prevalence after age 60 [92]. There are very few studies that have directly examined differences in the prevalence of OSA by race or ethnicity, and those only compared African Americans with whites. However, from the available literature, it appears that both younger and older African Americans are more likely to have OSA compared to whites [98, 99]. In Hispanics, the prevalence of OSA was estimated to be higher than that of whites based on overnight oximetry [96]. However, based on unattended home sleep studies the prevalence of OSA in US Hispanics was similar to that of whites [41]. The prevalence of symptomatic OSA in Asians has been reported similar to that of whites [37, 100–103]. There is a temporal trend of increasing OSA prevalence over time. The OSA prevalence in the general population that was described by Young et al. in 1993 (4 % for men and 2 % for women) is still quite commonly cited by sleep researchers and clinicians today [37]. However, with the obesity epidemic [86, 91] and the aging of the population, it is highly likely that the prevalence of OSA in the US has increased. Our most recent estimates of OSA prevalence come from the mostly white population of the Wisconsin Cohort Study in 2013 (Tables 14.1 and 14.2) and the direct measurements in the Hispanics Community Health Study/Study of Latinos in 2014, showing a definite increase in the prevalence of OSA over time [41, 91, 98].

Methodological differences make it challenging to compare earlier and later studies of OSA prevalence because of changes in measurement of hypopneas. Earlier sleep recordings utilized primarily the thermistor to evaluated airflow [37], which is notable for underestimating hypopneas, while later studies have used primarily the nasal cannula pressure transducer which is a better detector of hypopneas and airflow limitation [104, 105]. Also, earlier studies used "discernible" reductions in flow to identify hypopneas [37], while later studies have used more precise airflow decrements of 30 and 50 % detected by nasal cannula pressure transducers [51]. Moreover, earlier studies generally utilized a ≥4 % oxyhemoglobin desaturation to designate hypopneas [37], while later studies have also used the 2007 American Academy of Sleep Medicine alternate definitions of hypopneas that included a ≥3 % desaturation and/or a resultant arousal [51]. In all, the prevalence of OSA in the US population is probably significantly greater now than that reported in 1993 due to a true increase in OSA severity caused by the obesity epidemic and the aging of the population, as well by more accurate detection of hypopneas due to advances in technology.

Disparities in the Clinical Presentation of OSA

The clinical presentation of OSA differs significantly by sex. In a retrospective study, Shepertycky et al. evaluated 130 men and 130 women with OSA who were matched for age, BMI, AHI, and the ESS score. Both men and women presented similarly with respect to snoring and excessive daytime sleepiness. However, women were more likely to have a main presenting complaint of insomnia (odds

ratio 4.20; 95 % CI 1.54–14.26). Women were also more likely to endorse a history of depression (odds ratio 4.60; 95 % CI 1.71–15.49) and hypothyroidism (odds ratio 5.60; 95 % CI 2.14–18.57). Compared to their male counterparts, women were less likely to present with witnessed apnea and consumed less caffeine per day [106].

In the Sleep Heart Health Study, the severity of sleepiness increased with increasing OSA severity and with increasing frequency of snoring for both men and women, regardless of age or BMI [107, 108]. In a study that evaluated complaints of insomnia in men and women with OSA, women reported sleep onset insomnia more frequently than men (62 % vs. 53 %, $p=0.03$) as well as psychophysiologic insomnia (53 % vs. 45 %, $p=0.03$) more frequently than men [109].

In a more recent study of 384 African American and white adults that were evaluated with the Berlin Questionnaire [110], women with OSA reported fatigue more frequently than men with OSA (75 % vs. 46 %, $p<0.001$). In multivariate analysis that adjusted for potential confounders, men with OSA were sleepier than women, and African American men were significantly sleepier than white men (Average ESS 12.8 ± 5.2 for African American men as compared to 10.6 ± 5.3 for white men, $p=0.05$) [111]. In a retrospective study of 383 women and 661 men diagnosed with OSA, women were older and had a greater BMI and waist-to-hip ratio than men at the time of diagnosis. OSA severity based on respiratory disturbance index (RDI) was higher in men than women (41.2 ± 27.9 vs. 30.0 ± 26.7, $p<0.001$) despite a greater BMI in women [112]. In a population of 300 OSA patients (AHI > 10/h), the same investigative team again noted that women with OSA were older, had greater BMI, and had lower AHI at diagnosis compared to men [109].

Simpson et al. evaluated the relevance of fat distribution in men and women with OSA by measuring fat with dual-energy X-ray absorptiometry. The proportion of obese men and women did not differ (68 %, BMI > 30), and in evaluation of the upper airway, there was no difference in the proportion with a Mallampati score of III or IV by sex. In women, the combination of percentage of fat in the neck region and body mass index together explained 33 % of the AHI variance. In men, percentage of fat in the abdominal region and neck-to-waist ratio together accounted for 37 % of the AHI variance [113].

There are few studies directly evaluating ethnic/racial differences with respect to the clinical presentation of OSA. In a study by Scharf et al., African American OSA patients were younger at the time of diagnosis (44.9 ± 14.1 vs. 49.2 ± 14.5 years; $P=0.022$) and had greater BMI than whites (39.7 ± 10.7 vs. 33.4 ± 9.2 kg/m^2; $p<0.0001$). However, there was no difference in the severity of OSA between whites and African Americans after controlling for BMI and median household income [114]. Subramanian et al. evaluated the gender and ethnic differences in the prevalence of insomnia in 300 patients with OSA (AHI > 10/h) that included white, African American, and Hispanic men and women. White women were more likely to complain of sleep maintenance insomnia and Hispanic women were more likely to complain of psychophysiologic insomnia [109].

In summary, there are significant gender and racial/ethnic differences in the clinical presentation of OSA that could have diagnostic and therapeutic implications.

Like men, women with OSA present with snoring and excessive daytime somnolence [106–108]. However, women tend to be older, have a greater BMI [94, 109, 112], and demonstrate greater importance of neck fat in upper airway patency [113]. Women also present more frequently with a chief complaint of insomnia, fatigue, or depression, which can lead to a misdiagnosis or delayed diagnosis of OSA [109, 111]. Less data exist regarding the racial/ethnic differences in the clinical presentation of OSA. However, African Americans tend to be younger and more overweight at the time of diagnosis than whites. There does not appear to be a racial/ethnic difference in OSA severity at presentation [114]. More research is needed, especially comparing racial/ethnic differences in the clinical presentation of sleep-disordered breathing.

Disparities in the Clinical Effects of OSA

In epidemiological studies of the general population, African Americans have consistently higher ESS scores than non-Hispanic whites [65, 115, 116]. However, it is unclear if OSA has a differential effect based on gender or race/ethnicity. In multivariate analyses of subjects at high risk for OSA based on the Berlin Questionnaire, men were more sleepy than women, and African American men were significantly sleepier than white men ($p = 0.05$) [111]. In the same study, women at high risk for OSA reported fatigue more commonly than their male counterparts [111].

In the Sleep Heart Health Study, the health-related quality of life of white, African American, and Hispanic participants was compared using the Short Form-36 (SF-36) physical composite and mental composite scales. There were no ethnic/racial differences in the mental or physical health-related quality of life of subjects with moderate or more severe OSA (AHI > 15/h), suggesting that OSA may not have a differential effect on quality of life based on race or ethnicity in adults [66]. However, in the population-based TuCASA study, Hispanic children with sleep-disordered breathing experienced more frequent symptoms such as snoring, excessive daytime somnolence, witnessed apneas, and learning problems than did white children, suggesting a potential differential effect by ethnicity of OSA on symptoms among children [69].

The current literature suggests that changes in weight and exercise differentially affect the severity of OSA by sex. In the Sleep Heart Health Study, weight gain and weight loss affected the severity of OSA more dramatically in men after controlling for age, OSA severity, neck circumference, BMI, ethnicity, and waist-hip ratio [117]. In the same study population, vigorous physical activity of a least 3 h a week was protective against OSA primarily in men and in those who were obese as compared to women and subjects who were not obese [118].

With respect to cardiovascular risk related to OSA, this was also examined in the Sleep Heart Health Study, which followed 5422 participants for a median of 8.7 years. Men with OSA were at a higher risk of an ischemic stroke at all levels of OSA severity compared to women with OSA. Men had an estimated increase in stroke risk of 6 % for each unit increase in AHI, whereas in women, increased

risk of stroke was only observed in the setting of moderate to severe OSA (AHI > 25/h) [119].

In summary, there appear to be gender and racial differences in the clinical effects of OSA. In the general population, African Americans have consistently been shown to be sleepier than whites [65, 115, 116]. In the setting of OSA, men are significantly sleepier than women, and African American men are more sleepy than whites, while women complain of fatigue more often than men [111]. OSA does not appear to affect health-related quality of life scores differentially based on race/ethnicity in adults [66]. However, Hispanic children with OSA were more likely to have learning problems as compared to their white counterparts [69]. The literature also suggests that men with OSA are better protected by weight loss and exercise [117, 118], but they are also more affected by weight gain and have a higher risk for stroke than women [119].

Disparities in Diagnosis and Treatment of OSA

OSA is a common condition [37, 41, 62, 91]; however, it is suspected to be widely underdiagnosed. Moreover, disparities in the recognition and diagnosis of OSA are suspected. Young et al. examined the proportion of OSA underdiagnosis in the Wisconsin cohort ($n = 4925$), which is a population without significant barriers to sleep disorders healthcare. They estimated that only 7 % of women and 18 % of men with moderate to severe OSA had received a clinical diagnosis. The diagnosed proportion for those with mild OSA was even lower at 2 % for women and 10 % for men [120].

The Sleep Heart Health Study investigators evaluated the factors that drive clinical recognition rates and treatment of OSA. Male gender and BMI were the only factors that were associated with increased likelihood of physician diagnosis and OSA treatment. The investigators concluded that disparities existed in the diagnosis and treatment of OSA, especially in women and individuals with lower BMI [121]. The Hispanic Community Health Study/Study of Latinos recently reported that only 1.3 % of participants ($n = 14{,}400$) that underwent an unattended home sleep study had a prior diagnosis of OSA [41]. Of note, the prevalence of OSA (AHI ≥ 5/h) in this sample population was 25.8 % [41], suggesting an extremely low level of evaluation and diagnosis for OSA in Hispanics living in the US. The 2010 Sleep in America Poll was a national survey of 1007 Americans who identified themselves as white, African American, Asian, or Hispanic to compare the sleep health, attitudes, and knowledge about sleep across different racial/ethnic groups [39]. In this study, African-Americans reported a prior diagnosis of OSA (14 %) much more often than Hispanics (8 %), whites (6 %), or Asians (4 %) [122].

With respect to OSA treatment adherence, some studies have identified differences by gender and socioeconomic status. In a study of 507 patients with OSA (77 % African Americans), women were 2.49 (95 % CI 1.39–4.46) times more likely to be noncompliant with CPAP than men after adjusting for race, marital status, and age [123]. In a population of 266 veterans with OSA, daily CPAP use ≥4 h ranged

from 34.1 % (95 % CI, 26.4, 42.7) for subjects from a low socioeconomic neighborhood to 62.3 % (95 % CI 53.8, 70.1) for subjects from a high socioeconomic neighborhood, suggesting that noncompliance with CPAP was related to socioeconomic status [124]. Others have reported that patients with low socioeconomic status are less receptive to CPAP treatment after a 2-week trial [125] and less compliant with CPAP [126] than patients with higher socioeconomic status.

Race/ethnicity has also been evaluated as a factor in CPAP compliance. Scharf and colleagues reported no difference in the acceptance and long-term compliance of CPAP therapy between African Americans and whites [114]. However, Billings et al. reported that African Americans and those in lower socioeconomic residential areas demonstrated poorer adherence to CPAP as compared to whites and Hispanics after 1 and 3 months of follow-up, despite provision of standardized access to care and treatment in a clinical trial setting [126]. The mechanisms of such disparity were not evaluated.

In summary, it appears that men and obese individuals are more likely to be evaluated for OSA compared to women and individuals of lower BMI [121]. This disparity may be explained in part by poor awareness on the part of medical providers of the gender differences in the clinical presentation of OSA. Hispanics appear to have a high prevalence of underdiagnosed OSA, which may be explained by low access to medical care [41]. Women appear to be less adherent to CPAP than men. African Americans and those in lower socioeconomic groups appear to accept CPAP less readily and are less compliant with CPAP therapy than other ethnic or higher socioeconomic groups [123–126].

Mechanisms for Disparities in Sleep-Disordered Breathing

Few have attempted to determine the mechanisms for disparities in sleep-disordered breathing with respect to gender, age, socioeconomic status, or race/ethnicity. Most of the available literature on sleep-disordered disparities is based on retrospective or observational studies. Therefore, the available literature does not lend itself to mechanistic hypotheses testing.

With respect to potential biological mechanisms, gender differences in snoring and OSA in the premenopausal years have been attributed to the protective effects of estrogen [93, 127, 128]. Indeed, in animal and in vitro studies, estrogen upregulates genioglossus estrogen receptors and has a protective effect in the fatigability of genioglossus tissue exposed to intermittent hypoxia [129]. Also, women with a history of ovarihysterectomy who have OSA demonstrated significant AHI reduction after just 1 week of combination therapy of medroxyprogesterone acetate and conjugated estrogens [128]. The results have not been as dramatic in other studies, which have only shown a slight reduction of REM-related AHI with hormonal replacement therapy [130]. However, there is sufficient evidence to suggest that estrogen has a protective effect on sleep-disordered breathing that partially explains the lower prevalence of OSA in premenopausal women as compared to men of

comparable age and BMI [93, 127]. The sleep-disordered breathing protective effect of estrogen is lost during pregnancy, probably due to multiple factors that reduce oropharyngeal caliber, such as estrogen-induced upper airway edema, weight gain, and reduced lung volume [131, 132].

Testosterone is thought to play a role in the pathogenesis of OSA in men, and this may at least partially contribute to the gender disparity. Exogenous testosterone has been shown to mildly increase OSA in obese men with severe OSA [133]. A potential mechanism is increased upper airway collapsibility [134]. However, the evidence connecting testosterone and OSA in men is weak and based primarily on case reports [135].

Less is known about the mechanisms for the sleep-disordered breathing disparity observed among racial/ethnic groups. Proposed mechanisms include differences in genetics, cultural and environmental factors, patterns of obesity, and cephalometric differences. In the US, minority and low-socioeconomic-status groups are disproportionately affected by overweight and obesity at all ages, especially African Americans and Mexican Americans, which could predispose them to higher rates of sleep-disordered breathing [136]. However, the relationship of BMI to OSA in African Americans is of similar magnitude as that of whites, suggesting that obesity patterns alone do not explain the racial/ethnic disparities in OSA [99].

Craniofacial morphology has been primarily studied in whites, Chinese, and Japanese subjects. Among patients with OSA, craniofacial abnormality findings appear to be similar in all racial/ethnic groups, primarily showing low position of the hyoid bone [137], retrognathia [138], smaller cranial base [139], and increase in the craniocervical extension angle [140]. A few studies have compared craniofacial measurements associated with OSA directly between racial/ethnic groups. Between whites and African Americans, Cakirer et al. found that brachycephaly (head shape with wider lateral and shorter anterior–posterior dimensions) is associated with an increased AHI in whites but not in African-Americans [141]. Also, in whites both skeletal craniofacial restriction and soft tissue enlargement of the tongue and soft palate are associated with OSA, while in African Americans only soft tissue enlargement is a significant factor [99]. In contrast, Chinese with OSA show greater skeletal restriction, including micrognathia and retrognathia, and a shorter and steeper anterior cranial base than whites [142, 143]. Also, Chinese subjects have more severe OSA at lower BMI as compared to whites, suggesting that skeletal restriction factors may be more important for OSA risk in Asians [142–144].

Almost no work has been reported on nonbiological factors for sleep-disordered breathing, in spite of the fact that the environment is a strong risk factor for health [145]. Only one study in the literature has evaluated the environment and the risk of sleep-disordered breathing. Ansarin et al. analyzed data from the National Health and Nutrition Examination Survey (NHANES) survey of 5545 individuals 16 years of age and older. The sample consisted of 22.5 % Mexican Americans, 44.5 % whites, 22.5 % African Americans, and 7.2 % other Hispanics and multiracial participants. OSA was assessed by using questions on habitual snoring, witnessed apneas, and daytime sleepiness, and study investigators found that never repeating a school grade and separated marital status were each associated with less risk of

OSA. In contrast, having pets in the home or living in a home with mildew or musty smell was associated with a higher risk of OSA. Factors such as the type of home, number of persons living in the home, or the presence of pests such as cockroaches did not predict OSA [146].

In summary, in the premenopausal years, the disparity in OSA prevalence between men and women may be due to the protective effects of estrogen in women and potentially the deleterious effect of testosterone in men [93, 127–130, 135]. Greater rates of obesity are found in Mexican Americans, African Americans, and patients from low socioeconomic groups as compared to whites [136]. However, at least in the case of African Americans, obesity alone does not explain the higher prevalence of OSA as compared to whites [94]. Although the data are limited, the craniofacial differences existing between Asians, African Americans, and whites may explain some of the disparities in OSA prevalence and severity [137–143]. However, the available literature is not sufficient to determine the exact contribution of these factors to the observed gender and racial/ethnic differences in the prevalence and severity of OSA [147]. Very little information exists on nonbiological factors and the risk of OSA [145]. More research is needed before a firm conclusion can be made.

Conclusion

There are significant age, gender, racial/ethnic, and socioeconomic disparities in the prevalence, presentation, diagnosis, morbidity, and therapy of sleep-disordered breathing that may contribute to disparities in the health of the U.S. population. The prevalence of snoring is very common, increases with age, and is higher in Hispanics. OSA is strongly associated with being male, increasing age, and obesity, and it is more prevalent in African Americans than in whites, Asians, or Hispanics. African Americans are also younger, heavier, and more sleepy at diagnosis, which may predispose them to greater cardiovascular complications. Women complain more of insomnia, fatigue, and depression rather than sleepiness at presentation, which may lead to misdiagnosis or delay diagnosis of OSA, especially in those with lower BMI. The literature supports significant disparities in the morbidity of sleep-disordered breathing. Men with OSA are sleepier than women, and men are at a higher risk of stroke for every level of OSA severity. Also Hispanic children may be at a higher risk of cognitive impairment when they suffer from OSA. There are also disparities in the response to therapy for OSA. Weight changes and exercise produce a larger beneficial effect in the AHI of men as compared to women. Also lower CPAP compliance is seen in patients of lower socioeconomic status, African Americans, and women. Most of the research in sleep-disordered breathing disparities is observational and does not lend itself to mechanistic hypothesis testing. However, a protective effect of estrogen and deleterious effect of testosterone may partially explain the higher prevalence of OSA in men as compared to women. The racial/ethnic differences in OSA are more difficult to explain due to the scarcity of research in

this area. Higher BMI in minorities and subjects of lower socioeconomic status has been proposed as a contributing factor for OSA, but more research is needed before a firm conclusion can be reached. Also, craniofacial differences may contribute to OSA in Asians as compared to whites. Much more research is needed to fully elucidate and understand the observed disparities in the prevalence, presentation, diagnosis, morbidity, and therapy of sleep-disordered breathing.

References

1. Tobler I. Why do we sleep? Contributions from animal research. Ther Umsch. 2000;57(7): 417–20.
2. Siegel JM. Do all animals sleep? Trends Neurosci. 2008;31(4):208–13.
3. Mendelsohn AR, Larrick JW. Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases. Rejuvenation Res. 2013;16(6): 518–23.
4. Cirelli C, Tononi G. Is sleep essential? PLoS Biol. 2008;6(8), e216.
5. Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Night-day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens. 2009;23(10):645–53.
6. Rod NH, Kumari M, Lange T, Kivimäki M, Shipley M, Ferrie J. The joint effect of sleep duration and disturbed sleep on cause-specific mortality: results from the Whitehall II Cohort Study. PLoS One. 2014;9(4), e91965.
7. Baeck A, Rentmeesters N, Holtackers S, Op de Beeck HP. The effect of sleep in perceptual learning with complex objects. Vision Res. 2014;99:180–5. pii: S0042-6989(13)00238-1.
8. Potkin KT, Bunney Jr WE. Sleep improves memory: the effect of sleep on long term memory in early adolescence. PLoS One. 2012;7(8), e42191.
9. Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C. Effects of sleep and wake on oligodendrocytes and their precursors. J Neurosci. 2013;33(36):14288–300.
10. Aserinsky E. The discovery of REM sleep. J Hist Neurosci. 1996;5(3):213–27.
11. John 11:11-14, King James Version (KJV), 1611, public domain.
12. Pikovsky O, Oron M, Shiyovich A, Perry ZH, Nesher L. The impact of sleep deprivation on sleepiness, risk factors and professional performance in medical residents. Isr Med Assoc J. 2013;15(12):739–44.
13. Day A, Haj-Bakri S, Lubchansky S, Mehta S. Sleep, anxiety and fatigue in family members of patients admitted to the intensive care unit: a questionnaire study. Crit Care. 2013;17(3):R91.
14. Prather AA, Bogdan R, Hariri AR. Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. Psychosom Med. 2013;75(4):350–8.
15. Dlugaj M, Weinreich G, Weimar C, Stang A, Dragano N, Wessendorf TE, Eschler H, Winkler A, Wege N, Moebus S, Möhlenkamp S, Erbel R, Jöckel KH. Sleep-disordered breathing, sleep quality, and mild cognitive impairment in the general population. J Alzheimers Dis. 2014;14:479–97.
16. Logue EE, Scott ED, Palmieri PA, Dudley P. Sleep duration, quality, or stability and obesity in an urban family medicine center. J Clin Sleep Med. 2014;10(2):177–82.
17. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension. 2006;47: 833–9.
18. Ayas NT, White DP, Manson JE, Stampfer MJ, Speizer FE, Malhotra A, Hu FB. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med. 2003;163:205–9.

19. Simpson N, Dinges DF. Sleep and inflammation. Nutr Rev. 2007;65(Suppl):244–52.
20. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Prog Cardiovasc Dis. 2009;1:294–302.
21. Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. Sleep Med Rev. 2012;1:137–49.
22. Gastaut H, Tassinari CA, Duron B. [Polygraphic study of diurnal and nocturnal (hypnic and respiratory) episodal manifestations of Pickwick syndrome]. Rev Neurol (Paris). 1965;112(6):568–79.
23. Kapur VK, Redline S, Nieto FJ, Young TB, Newman AB, Henderson JA, Sleep Heart Health Research Group. The relationship between chronically disrupted sleep and healthcare use. Sleep. 2002;25(3):289–96.
24. Shepard Jr JW. Hypertension, cardiac arrhythmias, myocardial infarction, and stroke in relation to obstructive sleep apnea. Clin Chest Med. 1992;13:437–58.
25. Schäfer H, Koehler U, Ewig S, Hasper E, Tasci S, Lüderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. Cardiology. 1999;92(2):79–84.
26. Sell RE, Bardwell W, Palinkas L, Ancoli-Israel S, Dimsdale J, Loredo JS. Ethnic differences in sleep-health knowledge. Sleep. 2009;32(Abstract Suppl):A392.
27. Khoo MC, Gottschalk A, Pack AI. Sleep-induced periodic breathing and apnea: a theoretical study. J Appl Physiol (1985). 1991;70(5):2014–24.
28. Dempsey JA, Smith CA, Blain GM, Xie A, Gong Y, Teodorescu M. Role of central/peripheral chemoreceptors and their interdependence in the pathophysiology of sleep apnea. Adv Exp Med Biol. 2012;758:343–9.
29. Trinder J, Whitworth F, Kay A, Wilkin P. Respiratory instability during sleep onset. J Appl Physiol. 1992;73(6):2462–9.
30. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. Chest. 2007;131(2):595–607.
31. White DP. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med. 2005;172(11):1363–70.
32. Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, Edwards JK, White DP. Ventilatory control and airway anatomy in obstructive sleep apnea. Am J Respir Crit Care Med. 2004;170(11):1225–32.
33. Goldberg GR, Prentice AM, Davies HL, Murgatroyd PR. Overnight and basal metabolic rates in men and women. Eur J Clin Nutr. 1988;42(2):137–44.
34. Findley LJ, Ries AL, Tisi GM, Wagner PD. Hypoxemia during apnea in normal subjects: mechanisms and impact of lung volume. J Appl Physiol. 1983;55(6):1777–83.
35. Wilkinson V, Malhotra A, Nicholas CL, Worsnop C, Jordan AS, Butler JE, Saboisky JP, Gandevia SC, White DP, Trinder J. Discharge patterns of human genioglossus motor units during sleep onset. Sleep. 2008;31(4):525–33.
36. Prisk GK. Microgravity. Compr Physiol. 2011;1(1):485–97.
37. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230–5.
38. Baldwin C, Griffith KA, Nieto FJ, O'Connor G, Walsleben J, Redline S. Association of sleep disordered breathing and sleep symptoms with quality of life in The Sleep Heart Health Study. Sleep. 2001;24(1):96–105.
39. Masa JF, Rubio M, Findley LJ. Habitually sleepy drivers have a high frequency of automobile crashes associated with respiratory disorders during sleep. Am J Respir Crit Care Med. 2000;162:1407–12.
40. Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001;163(3 Pt 1):685–9.
41. Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, Youngblood M, Zee P, Daviglus ML. Sleep-disordered breathing in Hispanic/

Latino individuals of diverse backgrounds. The Hispanic Community Health Study/Study of Latinos. Am J Respir Crit Care Med. 2014;189(3):335–44.
42. Stepnowsky C, Johnson S, Dimsdale J, Ancoli-Israel S. Sleep apnea and health-related quality of life in African-American elderly. Ann Behav Med. 2000;22(2):116–20.
43. Ancoli-Israel S, Stepnowsky C, Dimsdale J, Marler M, Cohen-Zion M, Johnson S. The effect of race and sleep-disordered breathing on nocturnal BP "dipping": analysis in an older population. Chest. 2002;122(4):1148–55.
44. Profant J, Ancoli-Israel S, Dimsdale JE. Are there ethnic differences in sleep architecture? Am J Hum Biol. 2002;14:321–6.
45. Loredo JS, Soler X, Bardwell W, Ancoli-Israel S, Dimsdale JE, Palinkas LA. Sleep health in U.S. Hispanic population. Sleep. 2010;33(7):962–7.
46. Tomfohr L, Pung MA, Edwards KM, Dimsdale JE. Racial differences in sleep architecture: the role of ethnic discrimination. Biol Psychol. 2012;89(1):34–8.
47. Kingsbury JH, Buxton OM, Emmons KM, Redline S. Sleep and its relationship to racial and ethnic disparities in cardiovascular disease. Curr Cardiovasc Risk Rep. 2013;7(5):387–94.
48. Boss EF, Smith DF, Ishman SL. Racial/ethnic and socioeconomic disparities in the diagnosis and treatment of sleep-disordered breathing in children. Int J Pediatr Otorhinolaryngol. 2011;75(3):299–307.
49. 2003 National sleep disorders research plan. Sleep. 2003;26:253–7.
50. United States Census 2010. http://www.census.gov/2010census/.
51. Iber C, Ancoli-Israel S, Chesson A, Quan S; for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester: American Academy of Sleep Medicine; 2007.
52. Tamisier R, Pepin JL, Wuyam B, Smith R, Argod J, Levy P. Characterization of pharyngeal resistance during sleep in a spectrum of sleep-disordered breathing. J Appl Physiol. 2000;89(1):120–30.
53. Guilleminault C, Stoohs R, Clerk A, Simmons J, Labanowski M. From obstructive sleep apnea syndrome to upper airway resistance syndrome: consistency of daytime sleepiness. Sleep. 1992;15(6 Suppl):S13–6.
54. Exar EN, Collop NA. The upper airway resistance syndrome. Chest. 1999;115(4):1127–39.
55. Bao G, Guilleminault C. Upper airway resistance syndrome—one decade later. Curr Opin Pulm Med. 2004;10(6):461–7.
56. Guilleminault C, Kirisoglu C, Poyares D, Palombini L, Leger D, Farid-Moayer M, Ohayon MM. Upper airway resistance syndrome: a long-term outcome study. J Psychiatr Res. 2006;40(3):273–9.
57. Chen YH, Keller JK, Kang JH, Hsieh HJ, Lin HC. Obstructive sleep apnea and the subsequent risk of depressive disorder: a population-based follow-up study. J Clin Sleep Med. 2013;9(5):417–23.
58. Day R, Gerhardstein R, Lumley A, Roth T, Rosenthal L. The behavioral morbidity of obstructive sleep apnea. Prog Cardiovasc Dis. 1999;41(5):341–54.
59. Karimi M, Eder DN, Eskandari D, Zou D, Hedner JA, Grote L. Impaired vigilance and increased accident rate in public transport operators is associated with sleep disorders. Accid Anal Prev. 2013;51:208–14.
60. Schmidt-Nowara WW, Coultas DB, Wiggins C, Skipper BE, Samet JM. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. Arch Intern Med. 1990;150(3):597–601.
61. Ram S, Seirawan H, Kumar SK, Clark GT. Prevalence and impact of sleep disorders and sleep habits in the United States. Sleep Breath. 2010;14(1):63–70.
62. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. Chest. 2006;130(3):780–6.
63. Grandner MA, Petrov ME, Rattanaumpawan P, Jackson N, Platt A, Patel NP. Sleep symptoms, race/ethnicity, and socioeconomic position. J Clin Sleep Med. 2013;9(9):897–905.

64. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. Sleep. 1997;20(12):1077–85.
65. O'Connor GT, Lind BK, Lee ET, Nieto FJ, Redline S, Samet JM, Boland LL, Walsleben JA, Foster GL, Sleep Heart Health Study Investigators. Variation in symptoms of sleep-disordered breathing with race and ethnicity: the Sleep Heart Health Study. Sleep. 2003;26(1):74–9.
66. Baldwin CM, Ervin AM, Mays MZ, Robbins J, Shafazand S, Walsleben J, Weaver T. Sleep disturbances, quality of life, and ethnicity: the Sleep Heart Health Study. J Clin Sleep Med. 2010;6(2):176–83.
67. Ramos-Sepulveda A, Wohlgemuth W, Gardener H, Lorenzo D, Dib S, Wallace DM, Nolan B, Boden-Albala B, Elkind MS, Sacco RL, Rundek T. Snoring and insomnia are not associated with subclinical atherosclerosis in the Northern Manhattan Study. Int J Stroke. 2010;5(4):264–8.
68. Ramos AR, Wohlgemuth WK, Dong C, Gardener H, Wright CB, Boden-Albala B, Elkind MS, Sacco RL, Rundek T. Race-ethnic differences of sleep symptoms in an elderly multiethnic cohort: the Northern Manhattan Study. Neuroepidemiology. 2011;37(3–4):210–5.
69. Goodwin JL, Babar SI, Kaemingk KL, Rosen GM, Morgan WJ, Sherrill DL, Quan SF, Tucson Children's Assessment of Sleep Apnea Study. Symptoms related to sleep-disordered breathing in white and Hispanic children: the Tucson Children's Assessment of Sleep Apnea Study. Chest. 2003;124(1):196–203.
70. Goldstein NA, Abramowitz T, Weedon J, Koliskor B, Turner S, Taioli E. Racial/ethnic differences in the prevalence of snoring and sleep disordered breathing in young children. J Clin Sleep Med. 2011;7(2):163–71.
71. Frey WC, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. Obes Surg. 2003;13(5):676–83.
72. Rees K, Kingshott RN, Wraith PK, Douglas NJ. Frequency and significance of increased upper airway resistance during sleep. Am J Respir Crit Care Med. 2000;162(4 Pt 1):1210–4.
73. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest. 2002;121(5):1531–40.
74. Guilleminault C, Poyares D, Palombini L, Koester U, Pelin Z, Black J. Variability of respiratory effort in relation to sleep stages in normal controls and upper airway resistance syndrome patients. Sleep Med. 2001;2(5):397–405.
75. Pépin JL, Guillot M, Tamisier R, Lévy P. The upper airway resistance syndrome. Respiration. 2012;83(6):559–66.
76. Kristo DA, Lettieri CJ, Andrada T, Taylor Y, Eliasson AH. Silent upper airway resistance syndrome: prevalence in a mixed military population. Chest. 2005;127(5):1654–7.
77. Stoohs RA, Knaack L, Blum HC, Janicki J, Hohenhorst W. Differences in clinical features of upper airway resistance syndrome, primary snoring, and obstructive sleep apnea/hypopnea syndrome. Sleep Med. 2008;9(2):121–8.
78. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008;52(8):686–717.
79. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest. 1993;103(6):1763–8.
80. Fletcher EC, Lesske J, Qian W, Miller III CC, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. Hypertension. 1992;19(6 Pt 1):555–61.
81. Fletcher EC. Invited review: physiological consequences of intermittent hypoxia: systemic blood pressure. J Appl Physiol (1985). 2001;90(4):1600–5.
82. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: cross-

sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001; 163(1):19–25.
83. Mehra R, Benjamin EJ, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2006;173(8):910–6.
84. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, Sleep Heart Health Study Investigators. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol. 2004;160(6):521–30.
85. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Respirology. 2013;18(1):140–6.
86. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. Proc Am Thorac Soc. 2008;5(2):185–92.
87. Arnardottir ES, Maislin G, Schwab RJ, Staley B, Benediktsdottir B, Olafsson I, Juliusson S, Romer M, Gislason T, Pack AI. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. Sleep. 2012;35(7):921–32.
88. von Känel R, Loredo JS, Ancoli-Israel S, Dimsdale JE. Association between sleep apnea severity and blood coagulability: treatment effects of nasal continuous positive airway pressure. Sleep Breath. 2006;10(3):139–46.
89. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol. 2013; 62(7):569–76.
90. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009;6(8), e1000132.
91. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006–14.
92. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM, Sleep Heart Health Study Research Group. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002;162(8):893–900.
93. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med. 2001;163(3 Pt 1):608–13.
94. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med. 1994;149(3 Pt 1):722–6.
95. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community dwelling elderly. Sleep. 1991;14:486–95.
96. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40-64 years: a population-based survey. Sleep. 1997;20(1):65–76.
97. Sorlie PD, Avilés-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, Schneiderman N, Raij L, Talavera G, Allison M, Lavange L, Chambless LE, Heiss G. Design and implementation of the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol. 2010;20(8):629–41.
98. Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A, Fell R. Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med. 1995;152(6 Pt 1):1946–9.
99. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med. 1997;155(1):186–92.

100. Ip MS, Lam B, Lauder IJ, Tsang KW, Chung KF, Mok YW, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest. 2001;119(1):62–9.
101. Ip MS, Lam B, Tang LC, Lauder IJ, Ip TY, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. Chest. 2004;125(1):127–34.
102. Udwadia ZF, Doshi AV, Lonkar SG, Singh CI. Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. Am J Respir Crit Care Med. 2004;169(2):168–73. Epub 2003 Nov 6.
103. Kim J, In K, Kim J, You S, Kang K, Shim J, Lee S, Lee J, Lee S, Park C, Shin C. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med. 2004;170(10):1108–13.
104. Budhiraja R, Goodwin JL, Parthasarathy S, Quan SF. Comparison of nasal pressure transducer and thermistor for detection of respiratory events during polysomnography in children. Sleep. 2005;28(9):1117–21.
105. Redline S, Budhiraja R, Kapur V, Marcus CL, Mateika JH, Mehra R, Parthasarthy S, Somers VK, Strohl KP, Sulit LG, Gozal D, Wise MS, Quan SF. The scoring of respiratory events in sleep: reliability and validity. J Clin Sleep Med. 2007;3(2):169–200.
106. Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep. 2005;28(3):309–14.
107. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, Nieto FJ, Rosenberg CE. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. Am J Respir Crit Care Med. 1999;159(2):502–7.
108. Gottlieb DJ, Yao Q, Redline S, Ali T, Mahowald MW. Does snoring predict sleepiness independently of apnea and hypopnea frequency? Am J Respir Crit Care Med. 2000;162(4 Pt 1): 1512–7.
109. Subramanian S, Guntupalli B, Murugan T, Bopparaju S, Chanamolu S, Casturi L, Surani S. Gender and ethnic differences in prevalence of self-reported insomnia among patients with obstructive sleep apnea. Sleep Breath. 2011;15(4):711–5.
110. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131(7):485–91.
111. Eliasson AH, Kashani MD, Howard RS, Vernalis MN, Modlin RE; for the Integrative Cardiac Health Project Registry. Fatigued on Venus, sleepy on Mars-gender and racial differences in symptoms of sleep apnea. Sleep Breath. 2015;19:99–107. Epub ahead of print.
112. Subramanian S, Jayaraman G, Majid H, Aguilar R, Surani S. Influence of gender and anthropometric measures on severity of obstructive sleep apnea. Sleep Breath. 2012;16(4): 1091–5.
113. Simpson L, Mukherjee S, Cooper MN, Ward KL, Lee JD, Fedson AC, Potter J, Hillman DR, Eastwood P, Palmer LJ, Kirkness J. Sex differences in the association of regional fat distribution with the severity of obstructive sleep apnea. Sleep. 2010;33(4):467–74.
114. Scharf SM, Seiden L, DeMore J, Carter-Pokras O. Racial differences in clinical presentation of patients with sleep-disordered breathing. Sleep Breath. 2004;8(4):173–83.
115. Baron KG, Liu K, Chan C, Shahar E, Hasnain-Wynia R, Zee P. Race and ethnic variation in excessive daytime sleepiness: the multi-ethnic study of atherosclerosis. Behav Sleep Med. 2010;8(4):231–45.
116. Hayes AL, Spilsbury JC, Patel SR. The Epworth score in African American populations. J Clin Sleep Med. 2009;5(4):344–8.
117. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight. Arch Intern Med. 2005;165(20): 2408–13.

118. Quan SF, O'Connor GT, Quan JS, Redline S, Resnick HE, Shahar E, Siscovick D, Sherrill DL. Association of physical activity with sleep-disordered breathing. Sleep Breath. 2007;11(3):149–57.
119. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Tauqeer A, Lebowitz M, Punjabi NM. Obstructive sleep apnea hypopnea and incident stroke: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2010;182(2):269–77.
120. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997;20(9):705–6.
121. Kapur V, Strohl K, Dodge R, Iber C, Nieto FJ, O'Connor G, Redline S. Underdiagnosis of sleep apnea syndrome in U.S. communities. Sleep Breath. 2002;6(2):49–54.
122. National Sleep Foundation. 2010 Sleep in America Poll summary of findings. 2010. www.sleepfoundation.org.
123. Joo MJ, Herdegen JJ. Sleep apnea in an urban public hospital: assessment of severity and treatment adherence. J Clin Sleep Med. 2007;3:285–8.
124. Platt AB, Field SH, Asch DA, Chen Z, Patel NP, Gupta R, Roche DF, Gurubhagavatula I, Christie JD, Kuna ST. Neighborhood of residence is associated with daily adherence to CPAP therapy. Sleep. 2009;32(6):799–806.
125. Simon-Tuval T, Reuveni H, Greenberg-Dotan S, Oksenberg A, Tal A, Tarasiuk A. Low socioeconomic status is a risk factor for CPAP acceptance among adult OSAS patients requiring treatment. Sleep. 2009;32(4):545–52.
126. Billings ME, Auckley D, Benca R, Foldvary-Schaefer N, Iber C, Redline S, Rosen CL, Zee P, Kapur VK. Race and residential socioeconomics as predictors of CPAP adherence. Sleep. 2011;34(12):1653–8.
127. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, O'Connor GT, Rapoport DM, Robbins JA. Hormone-replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med. 2003;167(9):1186–92.
128. Pickett CK, Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Moore LG. Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. J Appl Physiol (1985). 1989;66(4):1656–61.
129. Lu Y, Liu Y, Li Y. Comparison of natural estrogens and synthetic derivative on genioglossus function and estrogen receptors expression in rats with chronic intermittent hypoxia. J Steroid Biochem Mol Biol. 2014;140:71–9.
130. Cistulli PA, Barnes DJ, Grunstein RR, Sullivan CE. Effect of short-term hormone replacement in the treatment of obstructive sleep apnoea in postmenopausal women. Thorax. 1994;49(7):699–702.
131. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. Clin Chest Med. 2011;32(1):175–89.
132. Venkata C, Venkateshiah SB. Sleep-disordered breathing during pregnancy. J Am Board Fam Med. 2009;22(2):158–68.
133. Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. Clin Endocrinol (Oxf). 2012;77:599–607.
134. Cistulli PA, Grunstein RR, Sullivan CE. Effect of testosterone administration on upper airway collapsibility during sleep. Am J Respir Crit Care Med. 1994;149(2 Pt 1):530–2.
135. Hanafy HM. Testosterone therapy and obstructive sleep apnea: is there a real connection? J Sex Med. 2007;4:1241–6.
136. Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. Epidemiol Rev. 2007;29:6–28.
137. Sakakibara H, Tong M, Matsushita K, Hirata M, Konishi Y, Suetsugu S. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. Eur Respir J. 1999;13(2):403–10.

138. Ishiguro K, Kobayashi T, Kitamura N, Saito C. Relationship between severity of sleep-disordered breathing and craniofacial morphology in Japanese male patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(3):343–9.
139. Albajalan OB, Samsudin AR, Hassan R. Craniofacial morphology of Malay patients with obstructive sleep apnoea. Eur J Orthod. 2011;33(5):509–14.
140. Ito D, Akashiba T, Yamamoto H, Kosaka N, Horie T. Craniofacial abnormalities in Japanese patients with severe obstructive sleep apnoea syndrome. Respirology. 2001;6(2):157–61.
141. Cakirer B, Hans MG, Graham G, Aylor J, Tishler PV, Redline S. The relationship between craniofacial morphology and obstructive sleep apnea in whites and in African-Americans. Am J Respir Crit Care Med. 2001;163(4):947–50.
142. Liu Y, Lowe AA, Zeng X, Fu M, Fleetham JA. Cephalometric comparisons between Chinese and Caucasian patients with obstructive sleep apnea. Am J Orthod Dentofacial Orthop. 2000;117(4):479–85.
143. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, Cistulli PA. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep. 2010;33(8):1075–80.
144. Sutherland K, Lee RW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. Respirology. 2012;17(2):213–22.
145. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23:303–31.
146. Ansarin K, Sahebi L, Sabur S. Obstructive sleep apnea syndrome: complaints and housing characteristics in a population in the United States. Sao Paulo Med J. 2013;131(4):220–7.
147. Villaneuva AT, Buchanan PR, Yee BJ, Grunstein RR. Ethnicity and obstructive sleep apnoea. Sleep Med Rev. 2005;9(6):419–36.

Chapter 15
Health Disparities in End-of-Life Care

Ann C. Long and J. Randall Curtis

Key Points

- High-quality end-of-life care should be available to all individuals faced with terminal illness.
- Differences in end-of-life care that are not driven by informed patient or family preferences may represent disparities in healthcare.
- Disparities in end-of-life care exist across race/ethnicity, socioeconomic status, sexuality, and underlying illness.
- Existing racial/ethnic disparities may be addressed by improving cultural competence among healthcare providers and enhancing communication about end-of-life care for nonwhite patients and their family members.
- Access to care is a major barrier to the delivery of quality end-of-life care to patients of lower socioeconomic status.
- Advance care planning is essential for members of the LGBT community and efforts to ensure equal rights for LGBT surrogate decision-makers must continue.
- Individuals with noncancer diagnoses are at risk for suboptimal palliative and end-of-life care.
- Future research is needed to elucidate mechanisms underlying disparities in end-of-life care and evaluate interventions targeted at improving both patient and family outcomes.

A.C. Long, M.D., M.S. (✉) • J.R. Curtis, M.D., M.P.H.
Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, 325 Ninth Avenue, Seattle, WA 98104, USA
e-mail: along11@uw.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_15

Introduction

Achieving excellence in end-of-life care requires a multifaceted approach involving high-quality communication, emotional support for patients and family members, and adequate control of patient symptoms during the dying process [1]. Accomplishing these goals is often challenging given the complex nature of medical decision-making at the end of life and the multitude of factors related to providers, patients, and healthcare systems that have the potential to affect delivery of care. For patients and family members, difficult decisions surrounding death and dying are made within a framework that incorporates characteristics unique to each individual. When well-informed patients and family members assert preferences about end-of-life care, differences are to be expected across a heterogeneous population. Thus, the exploration for disparity in end-of-life care often revolves around identifying differences that are not the result of an informed patient's preferences. End-of-life care that involves fewer elements of palliative care, more aggressive life-sustaining treatments, and limited symptom control may not represent preference-driven differences, but may instead represent healthcare disparity. Differences in informed preferences for end-of-life care should be respected, but differences in end-of-life care that are not driven by informed patient or family preferences must be addressed and intervened upon. In the following chapter, we examine differences in end-of-life care relative to gender, race/ethnicity, socioeconomic status (SES), sexuality, and underlying illness and consider explanations for identified differences.

Gender

Many of the described gender differences in end-of-life care relate to the intensity and aggressiveness of life-sustaining treatments provided prior to death and suggest that, compared to men, women are less likely to receive aggressive life-sustaining treatments at the end of life. This has been demonstrated in elderly patients with poor-prognosis malignancies, where women were less likely to receive chemotherapy in the last 14 days of life and had lower rates of in-hospital death [2]. In addition, hospice use appears to differ significantly between men and women, with timelier enrollment [2] and higher utilization among women [3–6]. One potential explanation for these gender differences relates to observed life expectancies of men and women. In general, men live shorter life spans than women [7]. Advanced age is associated with a higher prevalence of both chronic medical conditions and functional limitation [8]. Therefore women, dying at older ages than men, may be more likely to experience a progressive decline in health during their last years of life. Also, elderly women survive longer than men following the onset of significant disability, another factor influencing gender differences in the prevalence of chronic illness [9, 10]. Additional years spent in the setting of severe disability may

influence medical decision-making for elderly women and their family members, potentially prompting a shift away from aggressive life-sustaining treatments at the end of life. However, many of these observed gender differences in end-of-life care remain after adjustment for age, suggesting that differences in life expectancy do not completely explain these associations. Other factors are likely to be influential and thus must be examined when considering the potential for disparity.

Gender Differences in Social Support at the End of Life

Social support for patients and their family members is an important factor influencing quality of care at the end of life, and variation in levels of social support among men and women offers another potential explanation for observed gender differences in end-of-life care. Spousal support is a common source of informal caregiving for terminally ill patients, and marital status has been posited as an important mediator of the relationship between gender and many facets of end-of-life care [11]. Men frequently rely on female spouses for care at the end of life [12]. In contrast, elderly women are more likely than men to be widowed and often rely on other avenues of support [13]. Among lung cancer decedents, women were more likely to use social supportive services than men in the last year of life, potentially reflecting less robust informal caregiver support [14]. These differences in support systems may influence location of death [15] and this in turn may affect the characteristics of care provided to men and women at the end of life. The presence of gender differences in social support among elderly adults should prompt healthcare providers to ask specific questions regarding the availability of both formal and informal caregivers for patients with chronic illness and limited life expectancy. Furthermore, support should not only be assessed for the patient but also for the primary caregiver. The role of primary caregiver is often assumed by women, and evaluations of caregiver experiences suggest that women are more likely to report caregiver strain [16, 17]. Understanding the interplay between gender and social support may assist in addressing caregiver burden while also ensuring that adequate networks are in place to help achieve end-of-life care goals for dying patients and their family members.

Gender Differences in Preferences for End-of-Life Care

It is important to consider the possibility that men and women have differing attitudes about end-of-life care. Men report more favorable views of life-sustaining measures compared to women [18] and among young adults, men are less likely to report a positive opinion about hospice than women [19]. Whereas women seem more likely to have a higher level of trust in the healthcare system, men are more likely to express concern about incurring harm within the system [20], a sentiment

that may translate into reluctance to utilize hospice and palliative care services and distrust of offers related to limited intervention. In addition to gender differences in attitudes and knowledge about end-of-life care, men and women also demonstrate different understandings of terminal illness. In a study of patients with advanced cancer, when compared with men, women improved the accuracy of their medical knowledge with progression of time and were also more likely to report having conversations about life expectancy with their oncologists [21]. Some of these differences may relate to variability in the styles of communication and emotional support that men and women prefer, but more information is needed to assist in development of a clear understanding of the nature of gender differences in values, beliefs, and knowledge surrounding end-of-life care.

Summary: Gender

Gender differences in end-of-life care are influenced by a complex interplay of age, chronic illness and disability, social support networks, and values and beliefs. It is difficult to know if any of the aforementioned differences represent disparities, but they do represent elements of end-of-life care that may require special attention from providers. Women live longer than men and often face significant functional limitation at the time of death without the support of a spouse. Women also frequently serve as the primary caregivers for their male spouses and may have unrecognized caregiver strain. Concerted efforts to evaluate social support networks for elderly patients and those with chronic illness should be universal, but may require different approaches based upon gender differences. In an ideal setting the achievement of end-of-life care goals would be directed by informed patient preferences and not by life circumstances that affect the social support available to dying patients and their family members. Finally, additional research is required in order to explain observed discrepancies between men and women regarding perceptions of hospice and preferences for aggressive life-sustaining treatments. A better understanding may allow healthcare providers to tailor communication about the nature of palliative and end-of-life care to meet the differing needs of men and women.

Race and Ethnicity

There is significant evidence of racial and ethnic differences in end-of-life care, including differences in communication practices, advance care planning, and the characteristics of care provided prior to death. In addition, attitudes about end-of-life care and patient preferences related to receipt of life-sustaining treatments also differ significantly across race/ethnicity. In general, individuals of nonwhite race/ethnicity receive more aggressive life-sustaining treatments at the end of life. Among patients age 65 and older, African-Americans, Asians, and Hispanic patients

are less likely than whites to have do not attempt resuscitation (DNAR) orders in place within the first 24 h after hospital admission [22], and compared to whites, African-Americans are more likely to be "full code" at the end of life [23] and die in the setting of full support [24]. Observed differences in hospice utilization suggest lower use among patients of nonwhite race/ethnicity [25, 26], and African-Americans who do enroll in hospice are more likely than whites to revoke hospice in pursuit of aggressive care [27] and less likely to return to hospice after leaving [28]. Much of the excess cost of end-of-life care observed for African-American and Hispanic patients has been attributed to ICU admissions and receipt of life-sustaining interventions at the end of life [29]. To understand the observed associations between race/ethnicity and end-of-life care, it is helpful to begin by exploring the relationship between race/ethnicity and communication about end-of-life care.

Differences in Communication about End-of-Life Care by Race/Ethnicity

A fundamental component of quality end-of-life care includes clear communication with patients and their family members about a patient's medical illness, overall prognosis, and goals of care. In order to make an informed decision about treatment preferences, patients and their family members must be provided with information that facilitates an appreciation of the issues at hand. If this task cannot be accomplished for patients with life-limiting illnesses, the likelihood that they will make informed decisions is low. Active communication between physicians and patients is essential but the quality of this communication may differ by race/ethnicity. In general healthcare settings, African-American patients rate their visits with physicians as less participatory [30], and patients experiencing racially discordant physician interactions engage less with physicians and receive less information during visits [31]. Similar communication disparities have been identified in end-of-life care. Family members of African-American decedents are more likely than those of white decedents to express concerns about being informed or cite absent or problematic communication with physicians [32], and hospitalized African-American patients are less likely than patients of other races to have communication about cardiopulmonary resuscitation (CPR) preferences [33].

Racial/ethnic differences in advance care planning may also be related to inadequate communication with healthcare providers. Compared to whites, African-American and Korean Americans are less likely to have knowledge about advance directives, including living wills and the concept of a durable power of attorney [34]. Though sociocultural differences may play a role in shaping the characteristics of conversations that patients and their family members have with healthcare providers, it is difficult to imagine that individuals of nonwhite race/ethnicity prefer less participatory conversations about end-of-life care or wish to be less informed. A lack of information sharing that leaves patients and family members with limited knowledge about options for treatment and results in decision-making about end-of-life care that is not fully informed would represent disparities in care.

Differences in Preferences for and Attitudes about End-of-Life Care by Race/Ethnicity

Poor quality communication is unlikely to reflect patient preference, but it could be argued that some other observed racial/ethnic differences in end-of-life care do reflect patient choice. Patients of nonwhite race/ethnicity have been consistently demonstrated to prefer more aggressive life-sustaining treatments at the end of life [35–37], and numerous potential explanations have been provided for this observation. Spirituality and religion may factor prominently into end-of-life decisions for many nonwhite patients and their family members, where the concept of miracles and potential intervention from a higher power may promote requests for ongoing aggressive measures and where efforts to limit therapies at the end of life may be viewed as conflicting with deeply held spiritual beliefs [38–40]. Cultural norms regarding the decision-making role of family members may also affect choices made about life-sustaining interventions. For example, among Korean-American decisions regarding life-sustaining measures might be deferred to family members in order to respect the notion of filial piety, even if the patient or family member has their own personal preferences regarding aggressive care at the end of life [39]. Importantly, patient preferences may also be shaped by mistrust in a healthcare system that has participated in mistreatment of individuals of nonwhite race/ethnicity [40, 41].

In addition, negative attitudes about advance care planning have been identified among African-Americans [42], and these attitudes may influence the likelihood that patients complete such planning. Compared to whites, African-American patients are less likely to have completed a living will prior to death or to have appointed a durable power of attorney for health [43–45], and among nursing home residents nonwhite patients are less likely than non-Hispanic whites to have living wills, DNAR orders, or surrogate decision-makers [46–49]. However, there is evidence to suggest that limited participation in advance care planning may not simply be a reflection of patient preference. African-American patients who have conversations about end-of-life care with their physicians are more likely to have DNAR orders in place than those who do not [50]. This would suggest that the failure to actively engage nonwhite patients in communication about end-of-life care might shape the characteristics of the care they receive.

Summary: Race/Ethnicity

Race/ethnicity and culture do play a significant role in shaping preferences for end-of-life care [37, 51], and it is important for healthcare providers to understand these factors in order to provide the best quality end-of-life care for patients and their family members. However, patient preferences alone are unlikely to fully account for racial/ethnic differences in end-of-life care. As previously noted,

communication about end-of-life care plays a significant role in the decision-making process for patients and families, and a lack of information affects the ability to make informed decisions. Mistrust in the healthcare system, coupled with a poor understanding of available palliative care services [52, 53], could potentially be addressed by enhanced communication with patients of nonwhite race/ethnicity. Indeed, interventions to enhance patient understanding of treatment options may attenuate differences in choices about end-of-life care that might otherwise be reflexively attributed to patient preferences [54]. Healthcare providers must make a concerted effort to acknowledge the influence and importance of culture on end-of-life care decision-making, while simultaneously ensuring that the treatment decisions of nonwhite patients and their family members are made in the context of appropriate communication. Given a historical background of racial discrimination and exploitation within the healthcare system, expressed preferences that might result in poor quality of life or limited control of pain and suffering at the end of life should be thoroughly scrutinized before being attributed to sociocultural norms.

Socioeconomic Status

In the study of healthcare outcomes, SES (often measured as income, and/or education level) and race/ethnicity are often related, with similar associations seen between outcomes of interest and these different predictors. However, conflation of SES and race/ethnicity can diminish the importance of each and hinder efforts to improve outcomes for patients and family members. Associations between race/ethnicity and end-of-life care are often found to be independent of SES, and vice versa. Though individuals with lower levels of income and education may experience end-of-life care that shares similarities with the end-of-life care described for individuals of nonwhite race/ethnicity, healthcare providers should take care not to assume that the mechanisms underlying associations between race/ethnicity and end-of-life care are identical to those observed for SES.

Differences in Delivery End-of-Life Care by Socioeconomic Status

Poverty has long been associated with poor quality health and worse healthcare outcomes, and inadequate education and limited access to care may serve as underlying determinants of these outcomes among the poor [55]. In addition to limited access to general healthcare services, evidence suggests that individuals of lower SES also face similar barriers to care at the end of life [56]. Assessments of sociodemographic factors suggest that those of lower SES [26] and those with no or limited insurance [57, 58] underutilize hospice care at the end of life. Although a lack of

financial resources does not preclude enrollment in hospice or utilization of palliative care services, the poor may face challenges not experienced by those with higher SES, including limited access due to out-of-pocket costs associated with hospice care or absence of the social support necessary for hospice care. Similarly, death at home may be difficult for those with few financial resources or limited support systems. Patients with higher SES are more likely to die at home [59], and individuals with lower income who do receive home hospice services are more likely to transfer to another location prior to death [60]. Many individuals with terminal illness would prefer to spend their last days of life at home [61], but this may not be possible for those who lack financial and social support.

Planning and Preferences for End-of-Life Care by Socioeconomic Status

Advance care planning and patient preferences for end-of-life care also differ by SES. Those of higher SES are more likely to participate in advance care planning than those with lower SES [62, 63], an association that may be explained in part by financial planning among individuals with more material assets [62]. Language used in advance care planning documents is another important factor to consider. Lower SES has been associated with inadequate health literacy among older adults [64], and poor literacy may be a significant barrier to completion of legal documents that are often written above a 12th-grade reading level [65]. Health literacy has also been identified as an independent predictor of patient preferences regarding end-of-life care, with individuals of lower health literacy preferring more aggressive life-sustaining treatments [66]. Low health literacy may impair a patient's ability to comprehend information about diagnosis and prognosis, and thus lead to uncertainty in decision-making about end-of-life care [67]. Importantly, efforts to enhance patient understanding through nonverbal approaches may attenuate differences in end-of-life preferences related to low health literacy [66, 67].

Summary: Socioeconomic Status

SES has a wide range of influences on end-of-life care, and those of lower SES represent a vulnerable patient population. The ability to have treatment preferences honored and to achieve a satisfactory quality of dying should not be predicated upon a patient's social status, but differences in end-of-life care across levels of income and education suggest that this is not the reality for many patients and their family members. Improvements in resource allocation will require a broader commitment to equitable end-of-life care from healthcare organizations and financial stakeholders. From the standpoint of healthcare providers, targeted approaches to addressing end-of-life care needs for patients with limited income and education are necessary, and further research is needed to better understand the mechanisms underlying the

observed socioeconomic disparities in end-of-life care. Currently available information regarding the importance of health literacy in the process of informed decision-making supports ongoing investigation into methods aimed at improving the quality of communication about end-of-life care for individuals at a socioeconomic disadvantage.

Lesbian, Gay, Bisexual, and Transgender

Many challenges exist for members of the lesbian, gay, bisexual, and transgender (LGBT) community at the end of life [68]. Despite efforts to affect social and political change, legal restrictions continue to significantly influence end-of-life care for members of the LGBT community, as do social stigmatization and discrimination. For married heterosexual couples, the right of surrogate decision-making may be automatically afforded to either member of a partnership if one member becomes unable to make medical decisions. However, same-sex marriage is not legal in many regions nor are domestic partnerships uniformly recognized, and LGBT individuals may not be identified as surrogate decision-makers for a same-sex partner who is incapacitated by illness or injury [65]. In addition to the fear of being marginalized during and after the deaths of their partners, LGBT individuals in some regions also have to contest with the significant potential for loss of shared financial and property interests, interests that would be recognized for married heterosexual couples. Thus, advance care planning may be necessary both to maintain decision-making authority over the care of a dying loved one and to ensure shared finances and property are not lost at the time of death [69].

In recent years, political action by LGBT individuals affected by legal restrictions on surrogate decision-making has spurred legislation to extend rights for visitation and end-of-life decisions on behalf of same-sex partners [70]. However, significant barriers to quality end-of-life care for the LGBT community remain [71]. In addition to ongoing legal battles to ensure equal care for all, a vested interest in research endeavors directed at LGBT issues in end-of-life care is important. Literature addressing the palliative and end-of-life care preferences of sexual minorities is limited [72], and a better understanding is necessary to improve outcomes for this patient population. When communicating with terminally ill patients and their loved ones, healthcare providers should make a concerted effort to avoid assumptions of heterosexuality in order to support LGBT patients and their family members as they navigate these disparities in end-of-life care.

Underlying Illness

Despite differences in underlying illness, patients with limited life expectancy share a similar need for high-quality palliative care at the end of life. Although the trajectory of terminal illness varies from patient to patient, in many cases overall

prognosis may be similarly poor across a spectrum of disease processes. However, quality of end-of-life care may differ significantly by underlying illness [73]. Specialist palliative care is more commonly utilized for patients with cancer, compared to patients with other life-limiting illnesses such as chronic obstructive pulmonary disease (COPD), heart failure, or dementia [74–77]. Prognostic uncertainty for noncancer patients, particularly those with COPD or heart failure, may serve as a significant barrier to initiation of palliative care [78] yet the failure to discuss treatment preferences may result in more aggressive care at the end of life for patients with noncancer diagnoses. Patient communication needs and concerns may differ according to underlying illness [79], but provision of palliative care or end-of-life care consistent with patient preferences shoulder occur regardless of disease process. A concerted effort is needed to improve the quality of palliative and end-of-life care provided to patients with noncancer diagnoses.

Conclusion

As the population ages and the burden of chronic illness increases, the need for end-of-life care services is only expected to grow. The failure to address existing disparities in end-of-life care will allow continued delivery of suboptimal care and result in poor quality of dying and death for patients with terminal illness. It is important, then, to consider which of the identified differences in end-of-life care across gender, race/ethnicity, SES, sexuality, and underlying illness truly represent disparity (Fig. 15.1). Many of the differences observed across gender may reflect variation in

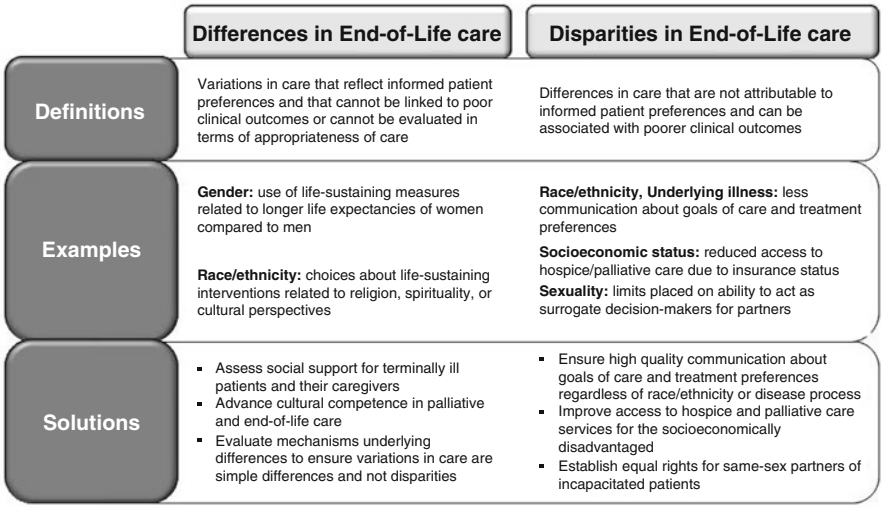

Fig. 15.1 Differences and disparities in end-of-life care: definitions, examples, and potential solutions

life expectancy and comorbidity among women and men, though evidence of gender differences in social support systems and caregiver roles should prompt specific focus on addressing how these factors influence the quality of end-of-life care for women and men. Racial and ethnic differences in end-of-life care present a more complicated issue, with evidence of poor communication for nonwhite patients and family members and end-of-life decisions that may be influenced by mistrust in the healthcare system. However, there are also important differences in preferences for end-of-life care by race/ethnicity and culture that must be honored and supported. Cultural competence in end-of-life care must be a priority for healthcare providers in order to improve communication for nonwhite patients and their family members and ensure respect for informed decisions that reflect patient and family preferences. Just as poverty affects many other healthcare outcomes, low SES also influences the quality of care that patients receive at the end of life. Underutilization of hospice and palliative care services by poor individuals and those without adequate insurance raises concerns for significant disparity in end-of-life care across levels of income. Similarly, limited education and poor health literacy represent barriers to receipt of high-quality end-of-life care. Addressing socioeconomic disparities in end-of-life care will require commitments from insurance agencies and health systems to attenuate differences related to financial constraints, and additional efforts to tailor communication about end-of-life care to patients with limited education or health literacy will be necessary. Disparity in end-of-life care for sexual minorities is prevalent. As efforts continue to secure equal rights for the LGBT community, healthcare providers should play an active role in sharing the importance of advance care planning for their LGBT patients and providing communication that is not biased by assumptions of heterosexuality. Finally, evidence of less frequent institution of palliative care for patients with noncancer diagnoses should promote efforts to improve communication and planning for these patients. Future research is needed to better understand the mechanisms underlying differences in end-of-life care across gender, race/ethnicity, SES, sexuality, and underlying illness, and additional study is necessary to more clearly define the relationship between these factors and patient and family outcomes.

References

1. Mularski RA, Curtis JR, Billings JA, et al. Proposed quality measures for palliative care in the critically ill: a consensus from the Robert Wood Johnson Foundation Critical Care Workgroup. Crit Care Med. 2006;34(11 Suppl):S404–11.
2. Miesfeldt S, Murray K, Lucas L, Chang CH, Goodman D, Morden NE. Association of age, gender, and race with intensity of end-of-life care for Medicare beneficiaries with cancer. J Palliat Med. 2012;15(5):548–54.
3. Lackan NA, Ostir GV, Freeman JL, Mahnken JD, Goodwin JS. Decreasing variation in the use of hospice among older adults with breast, colorectal, lung, and prostate cancer. Med Care. 2004;42(2):116–22.
4. Keating NL, Herrinton LJ, Zaslavsky AM, Liu L, Ayanian JZ. Variations in hospice use among cancer patients. J Natl Cancer Inst. 2006;98(15):1053–9.

5. Connor SR, Elwert F, Spence C, Christakis NA. Geographic variation in hospice use in the United States in 2002. J Pain Symptom Manage. 2007;34(3):277–85.
6. duPreez AE, Smith MA, Liou JI, et al. Predictors of hospice utilization among acute stroke patients who died within thirty days. J Palliat Med. 2008;11(9):1249–57.
7. Arias E. United States life tables, 2007. Natl Vital Stat Rep. 2011;59(9):1–60.
8. Lee SJ, Go AS, Lindquist K, Bertenthal D, Covinsky KE. Chronic conditions and mortality among the oldest old. Am J Public Health. 2008;98(7):1209–14.
9. Ferrucci L, Guralnik JM, Simonsick E, Salive ME, Corti C, Langlois J. Progressive versus catastrophic disability: a longitudinal view of the disablement process. J Gerontol A Biol Med Sci. 1996;51(3):M123–30.
10. Tiainen K, Luukkaala T, Hervonen A, Jylha M. Predictors of mortality in men and women aged 90 and older: a nine-year follow-up study in the vitality 90+ study. Age Ageing. 2013;42(4):468–75.
11. Wachterman MW, Sommers BD. The impact of gender and marital status on end-of-life care: evidence from the National Mortality Follow-Back Survey. J Palliat Med. 2006;9(2):343–52.
12. Emanuel EJ, Fairclough DL, Slutsman J, Alpert H, Baldwin D, Emanuel LL. Assistance from family members, friends, paid care givers, and volunteers in the care of terminally ill patients. N Engl J Med. 1999;341(13):956–63.
13. Jones AL, Harris-Kojetin L, Valverde R. Characteristics and use of home health care by men and women aged 65 and over. Natl Health Stat Rep. 2012;52:1–7.
14. Shugarman LR, Bird CE, Schuster CR, Lynn J. Age and gender differences in medicare expenditures and service utilization at the end of life for lung cancer decedents. Womens Health Issues. 2008;18(3):199–209.
15. Gomes B, Higginson IJ. Factors influencing death at home in terminally ill patients with cancer: systematic review. BMJ. 2006;332(7540):515–21.
16. Brazil K, Thabane L, Foster G, Bedard M. Gender differences among Canadian spousal caregivers at the end of life. Health Soc Care Community. 2009;17(2):159–66.
17. Fromme EK, Drach LL, Tolle SW, et al. Men as caregivers at the end of life. J Palliat Med. 2005;8(6):1167–75.
18. Bookwala J, Coppola KM, Fagerlin A, Ditto PH, Danks JH, Smucker WD. Gender differences in older adults' preferences for life-sustaining medical treatments and end-of-life values. Death Stud. 2001;25(2):127–49.
19. Webb NM, Tucker D. Young adults' opinions about hospice and home death. J Palliat Med. 2009;12(4):337–42.
20. Perkins HS, Cortez JD, Hazuda HP. Advance care planning: does patient gender make a difference? Am J Med Sci. 2004;327(1):25–32.
21. Fletcher K, Prigerson HG, Paulk E, et al. Gender differences in the evolution of illness understanding among patients with advanced cancer. J Support Oncol. 2013;11(3):126–32.
22. Richardson DK, Zive DM, Newgard CD. End-of-life decision-making for patients admitted through the emergency department: hospital variability, patient demographics, and changes over time. Acad Emerg Med. 2013;20(4):381–7.
23. Johnson RW, Newby LK, Granger CB, et al. Differences in level of care at the end of life according to race. Am J Crit Care. 2010;19(4):335–43; quiz 344.
24. Muni S, Engelberg RA, Treece PD, Dotolo D, Curtis JR. The influence of race/ethnicity and socioeconomic status on end-of-life care in the ICU. Chest. 2011;139(5):1025–33.
25. Cohen LL. Racial/ethnic disparities in hospice care: a systematic review. J Palliat Med. 2008;11(5):763–8.
26. Hardy D, Chan W, Liu CC, et al. Racial disparities in the use of hospice services according to geographic residence and socioeconomic status in an elderly cohort with nonsmall cell lung cancer. Cancer. 2011;117(7):1506–15.
27. Johnson KS, Kuchibhatla M, Tanis D, Tulsky JA. Racial differences in hospice revocation to pursue aggressive care. Arch Intern Med. 2008;168(2):218–24.
28. Kapo J, MacMoran H, Casarett D. "Lost to follow-up": ethnic disparities in continuity of hospice care at the end of life. J Palliat Med. 2005;8(3):603–8.

29. Hanchate A, Kronman AC, Young-Xu Y, Ash AS, Emanuel E. Racial and ethnic differences in end-of-life costs: why do minorities cost more than whites? Arch Intern Med. 2009;169(5):493–501.
30. Cooper-Patrick L, Gallo JJ, Gonzales JJ, et al. Race, gender, and partnership in the patient-physician relationship. JAMA. 1999;282(6):583–9.
31. Gordon HS, Street Jr RL, Sharf BF, Souchek J. Racial differences in doctors' information-giving and patients' participation. Cancer. 2006;107(6):1313–20.
32. Welch LC, Teno JM, Mor V. End-of-life care in black and white: race matters for medical care of dying patients and their families. J Am Geriatr Soc. 2005;53(7):1145–53.
33. Borum ML, Lynn J, Zhong Z. The effects of patient race on outcomes in seriously ill patients in SUPPORT: an overview of economic impact, medical intervention, and end-of-life decisions. Study to understand prognoses and preferences for outcomes and risks of treatments. J Am Geriatr Soc. 2000;48(5 Suppl):S194–8.
34. Murphy ST, Palmer JM, Azen S, Frank G, Michel V, Blackhall LJ. Ethnicity and advance care directives. J Law Med Ethics. 1996;24(2):108–17.
35. Degenholtz HB, Thomas SB, Miller MJ. Race and the intensive care unit: disparities and preferences for end-of-life care. Crit Care Med. 2003;31(5 Suppl):S373–8.
36. Barnato AE, Anthony DL, Skinner J, Gallagher PM, Fisher ES. Racial and ethnic differences in preferences for end-of-life treatment. J Gen Intern Med. 2009;24(6):695–701.
37. Krakauer EL, Crenner C, Fox K. Barriers to optimum end-of-life care for minority patients. J Am Geriatr Soc. 2002;50(1):182–90.
38. Born W, Greiner KA, Sylvia E, Butler J, Ahluwalia JS. Knowledge, attitudes, and beliefs about end-of-life care among inner-city African Americans and Latinos. J Palliat Med. 2004;7(2):247–56.
39. Blackhall LJ, Frank G, Murphy ST, Michel V, Palmer JM, Azen SP. Ethnicity and attitudes towards life sustaining technology. Soc Sci Med. 1999;48(12):1779–89.
40. Waters CM. Understanding and supporting African Americans' perspectives of end-of-life care planning and decision making. Qual Health Res. 2001;11(3):385–98.
41. Wicher CP, Meeker MA. What influences African American end-of-life preferences? J Health Care Poor Underserved. 2012;23(1):28–58.
42. Kwak J, Haley WE. Current research findings on end-of-life decision making among racially or ethnically diverse groups. Gerontologist. 2005;45(5):634–41.
43. Hopp FP, Duffy SA. Racial variations in end-of-life care. J Am Geriatr Soc. 2000;48(6):658–63.
44. Phipps E, True G, Harris D, et al. Approaching the end of life: attitudes, preferences, and behaviors of African-American and white patients and their family caregivers. J Clin Oncol. 2003;21(3):549–54.
45. Johnson KS, Kuchibhatla M, Tulsky JA. What explains racial differences in the use of advance directives and attitudes toward hospice care? J Am Geriatr Soc. 2008;56(10):1953–8.
46. Kiely DK, Mitchell SL, Marlow A, Murphy KM, Morris JN. Racial and state differences in the designation of advance directives in nursing home residents. J Am Geriatr Soc. 2001;49(10):1346–52.
47. Degenholtz HB, Arnold RA, Meisel A, Lave JR. Persistence of racial disparities in advance care plan documents among nursing home residents. J Am Geriatr Soc. 2002;50(2):378–81.
48. Reynolds KS, Hanson LC, Henderson M, Steinhauser KE. End-of-life care in nursing home settings: do race or age matter? Palliat Support Care. 2008;6(1):21–7.
49. Frahm KA, Brown LM, Hyer K. Racial disparities in end-of-life planning and services for deceased nursing home residents. J Am Med Dir Assoc. 2012;13(9):819.e7–11.
50. Mack JW, Paulk ME, Viswanath K, Prigerson HG. Racial disparities in the outcomes of communication on medical care received near death. Arch Intern Med. 2010;170(17):1533–40.
51. Crawley L, Payne R, Bolden J, Payne T, Washington P, Williams S. Palliative and end-of-life care in the African American community. JAMA. 2000;284(19):2518–21.
52. Yancu CN, Farmer DF, Leahman D. Barriers to hospice use and palliative care services use by African American adults. Am J Hosp Palliat Care. 2010;27(4):248–53.

53. Rhodes RL, Teno JM, Welch LC. Access to hospice for African Americans: are they informed about the option of hospice? J Palliat Med. 2006;9(2):268–72.
54. Benton K, Stephens J, Vogel R, et al. The influence of race on end-of-life choices following a counselor-based palliative consultation. Am J Hosp Palliat Care. 2015;32:84–9.
55. Wagstaff A. Poverty and health sector inequalities. Bull World Health Organ. 2002;80(2):97–105.
56. Lewis JM, DiGiacomo M, Currow DC, Davidson PM. Dying in the margins: understanding palliative care and socioeconomic deprivation in the developed world. J Pain Symptom Manage. 2011;42(1):105–18.
57. Rhodes RL, Xuan L, Paulk ME, Stieglitz H, Halm EA. An examination of end-of-life care in a safety net hospital system: a decade in review. J Health Care Poor Underserved. 2013;24(4):1666–75.
58. Mack JW, Chen K, Boscoe FP, et al. Underuse of hospice care by Medicaid-insured patients with stage IV lung cancer in New York and California. J Clin Oncol. 2013;31(20):2569–79.
59. Grande GE, Addington-Hall JM, Todd CJ. Place of death and access to home care services: are certain patient groups at a disadvantage? Soc Sci Med. 1998;47(5):565–79.
60. Barclay JS, Kuchibhatla M, Tulsky JA, Johnson KS. Association of hospice patients' income and care level with place of death. JAMA Intern Med. 2013;173(6):450–6.
61. Higginson IJ, Sen-Gupta GJ. Place of care in advanced cancer: a qualitative systematic literature review of patient preferences. J Palliat Med. 2000;3(3):287–300.
62. Carr D. The social stratification of older adults' preparations for end-of-life health care. J Health Soc Behav. 2012;53(3):297–312.
63. Rao JK, Anderson LA, Lin FC, Laux JP. Completion of advance directives among U.S. consumers. Am J Prev Med. 2014;46(1):65–70.
64. Sudore RL, Mehta KM, Simonsick EM, et al. Limited literacy in older people and disparities in health and healthcare access. J Am Geriatr Soc. 2006;54(5):770–6.
65. Castillo LS, Williams BA, Hooper SM, Sabatino CP, Weithorn LA, Sudore RL. Lost in translation: the unintended consequences of advance directive law on clinical care. Ann Intern Med. 2011;154(2):121–8.
66. Volandes AE, Paasche-Orlow M, Gillick MR, et al. Health literacy not race predicts end-of-life care preferences. J Palliat Med. 2008;11(5):754–62.
67. Volandes AE, Barry MJ, Chang Y, Paasche-Orlow MK. Improving decision making at the end of life with video images. Med Decis Making. 2010;30(1):29–34.
68. Smolinski KM, Colon Y. Silent voices and invisible walls: exploring end of life care with lesbians and gay men. J Psychosoc Oncol. 2006;24(1):51–64.
69. Hash KM, Netting FE. Long-term planning and decision-making among midlife and older gay men and lesbians. J Soc Work End Life Palliat Care. 2007;3(2):59–77.
70. Labella A, Singh D. Turning loss into legislation. Am J Public Health. 2008;98(6):971–3.
71. Wahlert L, Fiester A. A false sense of security: lesbian, gay, bisexual, and transgender (LGBT) surrogate health care decision-making rights. J Am Board Fam Med. 2013;26(6):802–4.
72. Harding R, Epiphaniou E, Chidgey-Clark J. Needs, experiences, and preferences of sexual minorities for end-of-life care and palliative care: a systematic review. J Palliat Med. 2012;15(5):602–11.
73. Wachter RM, Luce JM, Hearst N, Lo B. Decisions about resuscitation: inequities among patients with different diseases but similar prognoses. Ann Intern Med. 1989;111(6):525–32.
74. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax. 2000;55(12):1000–6.
75. Lau KS, Tse DM, Tsan Chen TW, Lam PT, Lam WM, Chan KS. Comparing noncancer and cancer deaths in Hong Kong: a retrospective review. J Pain Symptom Manage. 2010;40(5):704–14.
76. Beernaert K, Cohen J, Deliens L, et al. Referral to palliative care in COPD and other chronic diseases: a population-based study. Respir Med. 2013;107(11):1731–9.

77. Evans N, Pasman HR, Donker GA, Deliens L, Van den Block L, Onwuteaka-Philipsen B. End-of-life care in general practice: a cross-sectional, retrospective survey of 'cancer', 'organ failure' and 'old-age/dementia' patients. Palliat Med. 2014;28:965–75.
78. Dalgaard KM, Bergenholtz H, Nielsen ME, Timm H. Early integration of palliative care in hospitals: a systematic review on methods, barriers, and outcome. Palliat Support Care. 2014;13:1–19.
79. Curtis JR, Wenrich MD, Carline JD, Shannon SE, Ambrozy DM, Ramsey PG. Patients' perspectives on physician skill in end-of-life care: differences between patients with COPD, cancer, and AIDS. Chest. 2002;122(1):356–62.

Chapter 16
Where Do We Go from Here? Improving Disparities in Respiratory Health

Juan C. Celedón, Gary Ewart, and Patricia W. Finn

Key Points

- Health disparities adversely affect groups of people who have experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; occupation; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.
- Elimination of respiratory health disparities would not only alleviate major suffering but may also result in significant cost savings at the community, state, and federal levels.
- An uneven distribution of key modifiable risk factors for respiratory diseases across demographic groups is the main explanation for respiratory health disparities.
- Unequal access to or uneven quality of healthcare across demographic groups can lead to disparities in the burden of disease.
- Accomplishing respiratory health equality entails eliminating hazardous environmental and occupational exposures (achieving "environmental justice"), pro-

J.C. Celedón
Division of Pulmonary, Allergy and Immunology, Department of Pediatrics,
Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA, USA

G. Ewart
American Thoracic Society, Washington, DC, USA

P.W. Finn (✉)
Department of Medicine, University of Illinois at Chicago,
840 South Wood Street, 1020 N CSB, Chicago, IL 60612-7323, USA
e-mail: pwfinn@uic.edu

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*,
Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_16

moting a healthy lifestyle; and ensuring high-quality healthcare for all by broadening and facilitating access to a well-trained and diverse group of health providers. Achieving environmental justice and true universal high-quality healthcare are ultimately dependent on public policy, advocacy, education, and cutting-edge research.

- Building on programs created by the Affordable Care Act to ensure effective access to healthcare, as well as consistent data on minority health in the health system, is essential to truly improving healthcare access for minority populations.
- Universal access to the highest possible healthcare can only be achieved through research and innovations in disease prevention and treatment, ensuring a diverse and well-trained workforce of healthcare professionals in respiratory medicine, developing and updating clinical guidelines for all respiratory diseases (particularly those relevant to health disparities), and advocacy.
- Professional organizations must invest in educating and training their members to create a "lung corps" of effective advocates of respiratory health in general, and respiratory health equality in particular.

Introduction: A Call to Action

In the United States, the economically disadvantaged and members of certain ethnic minority groups (African Americans and Hispanics) have a shorter average lifespan (by as much as one to two decades [1]) than affluent or non-Hispanic white persons. This finding is explained by underlying disparities in health (including respiratory health) across these demographic groups.

Because the major risk factors for most diseases encountered in the practice of pediatric and adult pulmonary, critical care, and sleep medicine vary among demographic groups, respiratory health disparities are common [2, 3], as discussed in detail in earlier chapters of this book. Notable examples of disparities in respiratory diseases or related conditions include asthma [4, 5], chronic obstructive pulmonary disease (COPD) [6, 7], obesity (the strongest risk factor for obstructive sleep apnea) [8], lung cancer [9, 10], infectious and noninfectious pulmonary complications of human immunodeficiency virus (HIV) disease [11], cystic fibrosis (CF) [12], and sickle cell disease.

Current health disparities are not only morally unacceptable but financially unsound. From 2003 to 2006, elimination of existing health disparities across racial or ethnic groups could have saved over $1.2 trillion dollars in direct medical expenses and indirect costs related to disease and premature death [13]. Thus, the elimination of a major component of such disparities (those in respiratory health) would not only alleviate major suffering but also likely to result in significant cost savings at the community, state, and federal levels.

What Is Respiratory Health Equality?

The United Nations has recently focused on noncommunicable diseases (NCD) as significant contributors to the global burden of disease. In particular, respiratory NCDs (RNCDs), for example, COPD, asthma, and lung cancer are under scrutiny. In addition, professional organizations are striving to identify and develop approaches for tackling impediments to respiratory health, including health disparities.

Notably, the American Thoracic Society (ATS), a professional organization of over 15,000 members, recently defined respiratory health disparities as: "Significant differences in respiratory health that are closely linked to racial ancestry, social, economic, and/or environmental differences. Health disparities adversely affect groups of people who have experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; occupation; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion."

This definition was approved by the ATS Health Equality subcommittee, which also recently defined respiratory health equality as: "The attainment of the highest level of respiratory health for all people. Achieving health equality requires valuing everyone equally, implementing and maintaining focused societal efforts to address avoidable inequalities and historical and contemporary injustices, and eliminating health care disparities." To achieve this ideal goal, we must identify and eradicate the causes of respiratory health disparities.

What Are the Causes of Respiratory Health Disparities?

Most respiratory diseases are caused by hazardous environmental or lifestyle factors (Table 16.1). A few respiratory diseases are monogenic and thus exclusively caused by genetic variants (e.g., sickle cell disease), but the progression and severity of these diseases is often influenced by the environment. Thus, key modifiable risk factors for the vast majority of respiratory diseases include environmental and lifestyle risk factors, such as tobacco use, air pollution, and occupation. An uneven distribution of these determinants of respiratory health across demographic groups is the main explanation for respiratory health disparities.

A key concept in our understanding of respiratory health disparities is that exposure to environmental determinants of respiratory diseases is determined not only by an individual's choices but by "upstream" factors or "root causes" of both who is exposed and levels of exposure. Such root causes include societal and policy decisions, including those affecting regulation of relevant industries such as tobacco manufacturers and marketers, air quality, and the work environment. An example of an upstream determinant of respiratory health is the tobacco industry. Although

Table 16.1 Major environmental/lifestyle risk factors for respiratory health disparities in the United States

Risk factor	Impact
Tobacco smoke (direct or passive exposure)	Multiple respiratory illnesses, including asthma, chronic obstructive pulmonary disease (COPD), tuberculosis, and lung cancer
Air pollution	Morbidity and mortality from asthma and COPD
Intravenous drug use	Human immunodeficiency virus infection, pulmonary hypertension
Obesity	Obstructive sleep apnea, obesity-hypoventilation syndrome, asthma morbidity
Occupational hazards	Asthma, lung cancer, asbestosis, berylliosis, silicosis
Infections (e.g., influenza)	Pneumonia, acute respiratory failure, asthma, COPD

smoking can be portrayed as a "lifestyle" individual choice, this is not entirely true. The decision to become or remain a smoker is heavily influenced by marketing activities by the tobacco industry that are aimed to promote new smokers while having those who are nicotine-addicted remain active smokers. The industry's actions in marketing to particular demographic groups are well documented, including its success in increasing the number of female smokers after World War II, and in promoting menthol cigarettes among African Americans [14].

Air Pollution

While many policy makers often fail to see the connections, the environment is an important factor in health disparities. Air pollution, through roadways and industrial sources, occupational exposures, water quality, and an environment that does not promote exercise or proper nutrition are all key factors in health disparities. In the fight to improve our nation's air quality, professional organizations have played lead roles in advocating for stricter federal standards on ozone, particulate matter, mercury, and other air pollutants. As the Environmental Protection Agency (EPA) and state-level government organizations move toward implementing these stricter quality standards, all Americans, including minorities and low-income individuals, should enjoy the respiratory health and other benefits associated with clean air. While much progress has been made in clean air, individual physicians and professional organizations should continue to urge for science-based, clear standards to protect the public health.

Approximately 4 % of U.S. residents in 2010 lived close to (within 150 m) a major road and were thus heavily exposed to traffic-related air pollution [3], with a higher proportion of exposed individuals among non-Hispanic blacks (4.4 %) or Hispanics (5 %) than among non-Hispanic whites (3.1 %). Exposure to traffic-related air pollution is also correlated with living below the poverty level and being

foreign born [3]. Because traffic-related air pollution is associated with greater morbidity and mortality from asthma or COPD, it is a significant contributor to respiratory health disparities.

Members of ethnic minority groups and those with a lower educational status are more likely to be employed in occupations that expose them to a hazardous environment [2]. Since such occupations cause or worsen multiple respiratory diseases (including but not limited to asthma, silicosis, asbestosis, and berylliosis), occupation is an important determinant of respiratory health disparities.

In many cases, two or more environmental exposures that are more common in certain demographic groups interact to cause respiratory diseases and thus contribute greatly to respiratory health disparities. For example, a non-Hispanic black man without a high school diploma who is or was exposed to asbestos at work may also smoke cigarettes, putting himself at risk for COPD while also exponentially increasing his risk of lung cancer. Moreover, this individual may not have adequate access to preventive care and thus be at greater risk for communicable respiratory diseases such as influenza or pneumococcal pneumonia [2].

In addition to advocacy for sound public health policy, development and enhancement of programs aimed at educating the general public, patients suffering from respiratory diseases, and policy makers on the importance of eliminating or avoiding environmental hazards and adopting a healthy lifestyle are of utmost importance. For example, smoking is more common in those who do not finish high school—they may be more likely to be exposed to other risk factors (e.g., air pollution) but less likely to engage in a healthy lifestyle (e.g., maintaining normal body weight through exercise and a healthy diet) [15].

Given emerging threats to the environment and a healthy lifestyle, etiologic and interventional research on issues such as climate change, occupational hazards, nicotine delivery devices, and obesity is essential.

Tobacco

Current cigarette smoking differs across demographic groups (defined by gender, educational and socioeconomic status, sexual orientation, race or ethnicity, and area of residence [14, 16]) and causes or worsens multiple respiratory diseases (Table 16.1). Cigarette smoking is more common among the poor, and thrice as likely among adults who did not complete high school (31.5 %) as among those with a college degree (10.4 %) [14]. Over the last 40 years, active and passive exposure to tobacco smoke contributed to ~20.8 million premature deaths in the U.S., including ~10.4 million due to cancer and pulmonary diseases such as COPD [14]. From 2005 to 2009, current smoking caused 87 % and 61 % of all deaths from lung cancer and pulmonary diseases, respectively [14].

Tobacco use is the single largest preventable cause of death in the U.S. and takes a significant toll on minorities. Today, the physician and public health community are on the verge of having more effective tools to combat the ills of smoking. The

Food and Drug Administration (FDA) is proposing to exert regulatory authority over all tobacco products. These proposals include prohibition of the sales of tobacco products to anyone under the age of 18, including prohibition of vending machine sales, and registration of all manufacturers and ingredients. Additional proposals include elimination of free sampling of all tobacco products, good manufacturing practice requirements, premarket review for any "new" tobacco product or any product wishing to make a "modified risk or harm" claim, and user fees for all newly deemed products. If finalized, the above regulations should help reduce tobacco use in the U.S. and help address health disparities related to tobacco use among minority populations.

While important, what the FDA is proposing falls well short of the need. The FDA should take additional steps in addressing tobacco use, including: ban sweetened or candy flavored tobacco products and ban internet sales of tobacco products, as well as requiring child proof e-cigarette cartridges. With the notable rise in flavored cigar use among minorities, a ban on candy flavored tobacco products would reduce tobacco initiation among minority youth and would likely increase cessation efforts among current users.

Unfortunately, at the present time the FDA seems to be headed in a different direction. Indeed, the FDA has even proposed to exempt premium cigars from any FDA regulation. Under one of the options the FDA is considering, premium cigars (defined as hand-rolled whole leaf cigars costing more than $10) would be exempt from any FDA regulation, including warning labels, advertising and marketing restrictions, flavoring bans, misleading health claims, and ingredient disclosure. Healthcare workers, public health organizations, and health equality advocates need to seize this opportunity to ensure that the FDA finalizes a strong rule to protect the public, including minority populations, from disease and death caused by tobacco use.

Access to Healthcare

Once risk factors have led to the onset of a respiratory disease, unequal access to or uneven quality of healthcare across demographic groups can lead to disparities in the burden of such disease. In this context, high-quality healthcare comprises not only treatment but also prevention and screening for respiratory diseases. For example, preventive services such as vaccination against influenza can reduce the risk of complications from pulmonary diseases such as asthma or COPD, and detection of subclinical disease can strongly promote avoidance of hazardous environmental exposures (e.g., smoking in adolescents with alpha-1-antitrypsin deficiency [17]) or lead to early treatment (e.g., for lung cancer [18]).

It is not possible to ensure universal access to healthcare if barriers other than lacking health insurance are not removed, including inadequate health literacy or language skills, cultural beliefs, having no transportation to healthcare centers, missing clinical guidelines, and lack of cultural competency of healthcare providers. To complicate matters further, minority physicians, who provide medical care

for a significant proportion of underserved communities, are markedly underrepresented relative to the percentage of minorities in the U.S. population [19].

Figure 16.1 shows a causal framework for respiratory health disparities. An unhealthy environment or lifestyle, acting by itself or interacting with genetic variation, causes a respiratory disease. Whether that disease progresses or worsens is then affected by societal and environmental factors, including having high-quality healthcare, determined by root causes such as public policy, insurance, and education.

What Can Be Done to Achieve Respiratory Health Equality?

Achieving respiratory health equality can only be accomplished by vigorously addressing modifiable causes of health disparities (Fig. 16.1). Accomplishing respiratory health equality entails eliminating hazardous environmental and occupational exposures (achieving "environmental justice"), promoting a healthy lifestyle, and ensuring high-quality healthcare for all by broadening and facilitating access to a well-trained and diverse group of health providers. Achieving environmental justice and true universal high-quality healthcare are ultimately dependent on public policy, advocacy, education, and cutting-edge research (Fig. 16.2).

Accomplishing True Universal Healthcare

The Affordable Care Act (ACA) will give access to health insurance to millions of uninsured individuals, a laudable goal that will help reduce respiratory health disparities in the U.S. [20, 21]. However, a large number of people will remain uninsured in spite of the ACA (e.g., migrants without legal residency), and some barriers to healthcare access will still be unaddressed. Moreover, there is no cure for most respiratory diseases that disproportionately burden certain demographic groups.

While health disparities persist even when minority groups have health insurance, having health insurance does narrow the health disparities gap. Studies have shown that expanding health insurance positively impacts self-reported health status, improved financial security, and improves provision of preventative health services [22–24].

The ACA, when fully implemented, will have a significant impact on health disparities. Minorities are more likely to be uninsured than whites. For adults, 27 % of people of color are uninsured compared 15 % of whites. Hispanics have the highest uninsured rate at 33 % [25]. Through employer mandates, health insurance exchanges, federal subsidies, and optional Medicaid expansion (all backed by an individual mandate), the ACA will significantly expand health insurance coverage in the U.S.

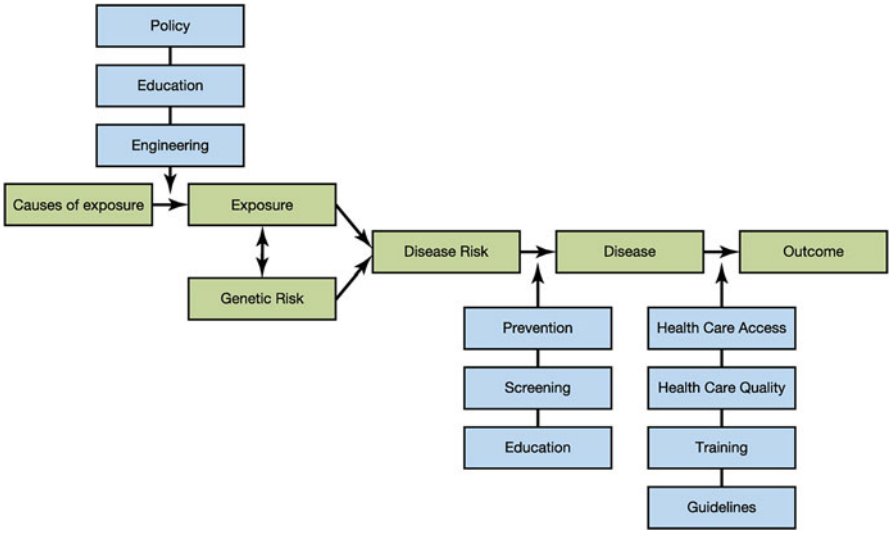

Fig. 16.1 Conceptual framework for the causality of respiratory diseases. Group differences at any stage in this pathway can lead to respiratory health disparities (adapted with permission of the American Thoracic Society. Copyright 2014 American Thoracic Society. Celedón JC et al. 2014. Respiratory health equality in the United States. The American thoracic society perspective. Ann Am Thorac Soc; 11: 473-9. Official Journal of the American Thoracic Society)

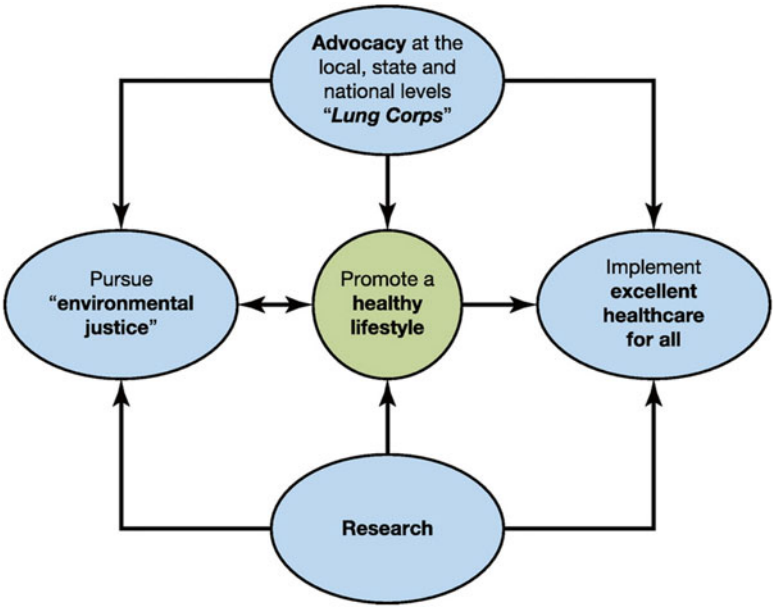

Fig. 16.2 Overview of the approach proposed by the American Thoracic Society to achieve respiratory health equality by eliminating existing disparities (adapted with permission of the American Thoracic Society. Copyright 2014 American Thoracic Society. Celedón JC et al. 2014. Respiratory health equality in the United States. The American thoracic society perspective. Ann Am Thorac Soc; 11: 473-9. Official Journal of the American Thoracic Society)

We detail here that the ACA holds promise for expanding health insurance, yet a considerable number of challenges are impeding implementation of the ACA. The first challenge involves issues around Medicaid expansion. As envisioned by Congressional supporters and the White House, the ACA was intended to require states to expand Medicaid insurance to adults at or below 138 % of the federal poverty level. However, states resistant to Medicaid expansion challenged what they felt was the coercive elements of the ACA Medicaid expansion. After mixed federal court rulings, the U.S. Supreme Court ultimately decided that Medicaid expansion was a state option. While this rule understandably was a shock to ACA supporters, in the long run, we may see the wisdom of the court's decision. When first enacted in 1965, Medicaid was an optional state/federal program to provide health insurance to the low income and disabled. While many states adopted Medicaid early on, it was not until 1972 that all states (except Arizona) participated in Medicaid. Arizona did not participate until 1982.

Medicaid expansion under the ACA will probably take a similar path. Over time, the ACA's generous matching funds for Medicaid expansion (100 % federal pay for the first 3 years and 90 %/10 % federal/state split after 3 years) will likely entice states to adopt Medicaid expansion. Undoubtedly, there will be states that take longer to adopt Medicaid expansion than others, due to local and national politics. Unfortunately, minorities and low-income individuals will likely pay a steep price in health status for states' delay. It is the role of healthcare workers, professional organizations, and advocates to communicate to state and federal policy makers that Medicaid expansion will play an essential role in addressing, but not fully resolving, health disparities at the local and national levels.

The second challenge focuses on specifics related to federal subsidies. While Medicaid expansion has received the majority of the attention, federal subsidies to enable families above the Medicaid threshold to purchase health insurance also play an essential role in providing health insurance to minority populations. The ACA will help this population (sometimes referred to as "near poor") purchase health insurance through state and federal exchanges. While the federal subsidies survived initial court challenges seeking to block subsidies for those who purchased insurance through federal exchanges, the provision of the subsidy is being complicated by other structural problems of the ACA legislation. Those who qualify for Medicaid or would qualify under state expansion, but live in a state that does not expand Medicaid, do not receive a federal subsidy to purchase health insurance.

The Kaiser Family Foundation estimates that 40 % of black uninsured adults will fall into this federal subsidy gap compared to 29 % of uninsured whites. Low-income adults who fall into this coverage gap are concentrated in states (e.g., Texas, Florida, and Georgia) who have chosen not to expand Medicaid. These three states alone will account for an estimated 1.2 million black adults and 1.0 million Hispanic adults falling into the federal subsidy gap [25]. The ACA waives the health insurance purchase and federal income tax penalty for low-income Americans. Thus, those who do not receive Medicaid expansion or the federal subsidy assistance will not get hit with a tax penalty, but they likely will not be able to afford health insurance either.

Further, if an employer offers health insurance, regardless of the affordability of the insurance offered, and their employees refuse the employer-provided health insurance, the employees are not eligible for the federal subsidy. This has led to an odd twist. In particular, some labor unions representing low-wage workers are now negotiating for employers NOT to offer health insurance because their union members would pay less for using a federal subsidy through the insurance exchange than they would if they participated in the plan offered by the employer [26].

Both these ACA drafting errors are fixable, but require Congress to act in a constructive fashion toward the ACA. The current Congress has voted over 50 times to repeal or defund ACA. They are in no mood to consider constructive improvements to ACA. The health community and other parties interested in addressing health disparities will need to be persistent, and patient, in urging Congress to fix the federal subsidy glitches.

Providing health insurance can reduce health disparities, but even with health insurance, health disparities exist. Again, the ACA has expanded programs that can address access to care beyond health insurance, including funding for community health centers; support for training for minority health professionals; and requirements for the collection of race, ethnicity, and language data across federal health programs. Building on these programs to ensure effective access to healthcare, as well as consistent data on minority health in the health system, is essential to truly improving healthcare access for minority populations.

Research

Universal access to the highest possible healthcare can only be achieved through research and innovations in disease prevention and treatment, ensuring a diverse and well-trained workforce of healthcare professionals in respiratory medicine, developing and updating clinical guidelines for all respiratory diseases (particularly those relevant to health disparities), and advocacy.

There is a need for a vibrant and dynamic national research agenda to achieve respiratory health equality by eliminating current disparities. This includes continued development and updating of clinical guidelines and workshop consensuses (which help identify gaps in knowledge and prioritize areas for investigation on health disparities), advocacy for research funding on health disparities by federal and nonfederal agencies, fostering and supporting community-based participatory research (including culturally appropriate interventions), and nurturing the careers of investigators focused on respiratory health disparities.

Started in 1990 as the Office of Minority Programs, the Institute of Minority Health and Health Disparities has grown in scope and funding. The Institute has grown from an annual budget of a few million as a center to an Institute with an annual budget of $262 million. While the increase in funding for minority health and health disparities is encouraging, the real impact of the Institute will be measured by how it influences sister NIH Institutes to include health disparities in their

portfolio. While progress on this front has been uneven, there are bright spots in respiratory research. Both the National Heart Lung and Blood Institute and National Institute of Allergy and Infectious Diseases are investing more funds in health disparities research. Physicians and professional organizations will need to leverage the influence of the National Institute for Minority Health and Health Disparities to ensure health disparities are part of a broader NIH agenda.

Ensuring a Diverse Workforce

Whereas the proportion of minority faculty in U.S. medical schools increased from ~7 % in 2000 to 8 % in 2010, the percentage of underrepresented minority individuals in the U.S. increased by more than 30 % during the same period [27]. Given that minority physicians play a major role in healthcare delivery to minority populations, fostering and maintaining a diverse workforce cannot be overlooked when developing strategies to achieve respiratory health equality.

Creation of a diverse workforce should involve a number of professional organizations interested in developing a pipeline of minority healthcare providers and researchers at several life stages (high school, college, and medical school), who can then be enticed to pursue careers in respiratory health. Young minority researchers in respiratory medicine should be given ample opportunities for education and training, so that they can competitively pursue the necessary funding to become independent investigators.

Mid-career and senior minority researchers should be part of decision-making bodies for funding by federal and nonfederal agencies.

Pursuing Environmental Justice and a Healthy Lifestyle

Exposures to certain environmental or lifestyle risk factors impact multiple respiratory diseases. Advocacy for policies that aim to reduce or eliminate such exposures is critical to reaching the goal of respiratory health equality.

Public health policy to accomplish environmental justice includes but is not limited to equal access to breathing clean air strong and sustained antismoking measures, and promotion and maintenance of a safe and healthy work environment. Because environmental justice would positively impact common nonrespiratory diseases (e.g., cancer and heart disease), involvement and advocacy by members of the public, patients, and multiple political and nonpolitical organizations is highly desirable. For example, effective communication between respiratory epidemiologists and the EPA is critical to inform EPA policies on air quality standards. Similarly, pulmonologists and their professional organizations strongly support regulation of tobacco products by the FDA.

Advocacy

Given that healthcare providers know little about advocacy, professional organizations must invest in educating and training their members to create a "lung corps" of effective advocates of respiratory health in general, and respiratory health equality in particular. Professional organizations and their members must continually advocate (at the local, state, and national levels) for increased access of all members of society to healthcare by primary care providers and specialists. Description of a "lung corps" has recently been provided [28]. It is essential to commit to national programs aimed to eliminate health disparities, giving particular emphasis to protecting the most vulnerable groups, including children (e.g., encouraging Medicaid expansion in all states) and migrant workers.

Conclusions

Environmental determinants of respiratory diseases are unevenly distributed across demographic groups, largely explaining major respiratory health disparities in the U.S. Achieving respiratory health equality entails elimination of modifiable environmental and lifestyle risk factors and universal high-quality healthcare. While progress has been made, much remains to be done in these areas. If we are to achieve respiratory health equality, all stakeholders must be involved: the public, patients affected by respiratory diseases, governmental and nongovernmental organizations, and professional organizations. Achieving respiratory health equality will be difficult but by no means impossible. As stated by Martin Luther King, Jr., we must act with the "fierce urgency of now." The next generation is counting on all of us.

Sources of Support Celedón: Grants HL079966, HL073373 and HL117191 from the U.S. National Institutes of Health, and an endowment from the Heinz Foundation.

Finn: Grant AI053878 from the U.S. National Institutes of Health.

References

1. Robert Wood Johnson Foundation. Commission Metro Map. Digital map. Commission to Build a Healthier America. The Robert Wood Johnson Foundation (RWJF); 2009. Accessed 10 Jan 2014.
2. Schraufnagel DE, et al. An official American Thoracic Society/European Respiratory Society policy statement: disparities in respiratory health. Am J Respir Crit Care Med. 2013;188(7):865–71.
3. Center for Disease Control and Prevention. CDC health disparities and inequalities report-United States, 2013. MMWR. 2013;62 Suppl 3:93–160.

4. Forno E, Celedon JC. Health disparities in asthma. Am J Respir Crit Care Med. 2012;185(10):1033–5.
5. Akinbami LJ, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief. 2012;94:1–8.
6. Silverman EK, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(6):2152–8.
7. Foreman MG, et al. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. Am J Respir Crit Care Med. 2011;184(4):414–20.
8. Ogden CL, et al. Prevalence of obesity in the United States, 2009–2010. NCHS data brief, no 82. Hyattsville, MD: National Center for Health Statistics; 2012.
9. Weeks JC, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367(17):1616–25.
10. Hayanga AJ, Zeliadt SB, Backhus LM. Residential segregation and lung cancer mortality in the United States. JAMA Surg. 2013;148(1):37–42.
11. Johnson AS, et al. HIV infection—United States, 2008 and 2010. MMWR Surveill Summ. 2013;62 Suppl 3:112–9.
12. Quon BS, et al. Disparities in access to lung transplantation for patients with cystic fibrosis by socioeconomic status. Am J Respir Crit Care Med. 2012;186(10):1008–13.
13. Joint Center for Political and Economic Studies. The economic burden of health inequalities in the United States. 2009. Washington, DC. Available at http://www.jointcenter.org/research/the-economic-burden-of-health-inequalities-in-the-united-states. Accessed 14 Jan 2014.
14. U.S. Department of Health and Human Services: The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
15. Centers for Disease Control and Prevention. CDC health disparities and inequalities report-United States, 2013. MMWR. 2013;62 Suppl 3:1–183.
16. Cochran SD, Bandiera FC, Mays VM. Sexual orientation-related differences in tobacco use and secondhand smoke exposure among US adults aged 20 to 59 years: 2003-2010 National Health and Nutrition Examination Surveys. Am J Public Health. 2013;103(10):1837–44.
17. Thelin T, Sveger T, McNeil TF. Primary prevention in a high-risk group: Smoking habits in adolescents with homozygous alpha-1-antitrypsin deficiency (ATD). Acta Paediatr. 1996;85:1207–12.
18. Humphrey LL, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. Ann Intern Med. 2013;159(6):411–20.
19. Marrast LM, et al. Minority physicians' role in the care of underserved patients: diversifying the physician workforce may be key in addressing health disparities. JAMA Intern Med. 2014;174:289–91.
20. US Department of Health and Human Services. Read the law: the Affordable Care Act, Section by Section. Washington, DC: US Department of Health and Human Services; 2012. Available at http://www.hhs.gov/healthcare/rights/law/index.html. Accessed 14 Jan 2014.
21. Congressional Budget Office. CBO's February 2013 estimate of the effects of the Affordable Care Act on health insurance coverage. Washington, DC: Congressional Budget Office; 2013. http://cbo.gov/sites/default/files/cbofiles/attachments/43900_ACAInsuranceCoverageEffects.pdf. Accessed 14 Jan 2014.
22. O'Hara B, Caswell K. Health status, health insurance, and medical services utilization: 2010. Current Population Reports; July 2013. p. P70-133RV.
23. Finkelstein A, Taubman S, Wright B, Bernstein M, Gruber J, Newhouse J, Allen H, Baicker K, Oregon Health Study Group. The Oregon Health Insurance experiment: evidence from the first year. Q J Econ. 2012;127(3):1057–106.

24. Bernstein J, Chollet D, Peterson S. How does health insurance coverage improve health outcomes? Princeton: Mathematica Policy Research; 2010. p. 1.
25. The impact of the coverage gap in states not expanding medicaid by race and ethnicity. Kaiser Family Foundation; 2013.
26. Ewart G. Ewart G personal communications with labor union staff.
27. Guevara JP, et al. Minority Faculty Development Programs and Underrepresented Minority Faculty Representation at US medical schools. JAMA. 2013;310(21):2297–304.
28. Thakur N, et al. The lung corps' approach to reducing health disparities in respiratory disease. Ann Am Thorac Soc. 2014;11(4):655–60.

ERRATUM TO

Chapter 7
Health Disparities in ARDS

Nancy Gonzalez Casanova, Jorge R. Navarrete, Hector Quijada, Louise Hecker, and Joe G.N. Garci

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_7

DOI 10.1007/978-3-319-23675-9_17

Louise Hecker's affiliation was missed in the published version of the book which was now included in the updated version. The affiliation is given below.

Louise Hecker, Ph.D
University of Arizona
Southern Arizona VA Health Care System
Department of Medicine
1656 E Mabel Street
Room 416
Tucson, AZ, 85724, USA
email: lhecker@email.arizona.edu
Supported by Veterans Administration Health System grant 1IK2BX001477 (L.H.).

The updated original online version for this chapter can be found at DOI http://dx.doi.org/10.1007/978-3-319-23675-9_7

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9_17

Index

L.B. Gerald, C.E. Berry (eds.), *Health Disparities in Respiratory Medicine*, Respiratory Medicine, DOI 10.1007/978-3-319-23675-9