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Health and Cognition in Old Age

From Biomedical and Life Course Factors to Policy and Practice

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Foreword

I am delighted to welcome and commend this volume on health and cognition in old age. Before extolling its virtues, let me explain its background. It is a product, indirectly, of the European Research Area in Ageing (ERA-AGE) which began in 2005 and will run until 2015 as Europe's ERA-NET in the ageing field (www.era-age.group.shef.ac.uk). During 2012 ERA-AGE reached 20 partners and associate partners all of whom are either national or regional research councils or ministries in 18 different countries.

Knowing that it is critical for Europe to build research capacity in this field, the ERA-AGE consortium decided to launch a completely new venture in European research: a postdoctoral programme funded jointly by different countries. The Future Leaders of Ageing Research in Europe (FLARE) was launched in 2007 with support from eight ERA-AGE members. A second call followed in 2010. Altogether 33 three-year postdoctoral fellowships were funded by nine countries. (The commissioning processes for both open calls for proposals were managed superbly by staff at the University of Sheffield.)

The FLARE Programme is unique: not only does it stipulate that there must be geographical mobility as part of each fellowship but also disciplinary mobility. I know from my observations during the FLARE Summer Schools organised by ERA-AGE that these fellows are a very special cohort of early-career researchers. FLARE aptly describes their quality and potential and this volume is a clear demonstration of their future leader status.

As well as the high quality of the contributions and the enthusiastic commitment of the editors to ageing research, four features of the book mark it out as an important contemporary work of gerontology. First, there is its emphasis on health, cognition, and well-being. The editors and contributors recognise that, while previous generations of researchers were focused on extending life expectancy, the urgent current concern must be to ensure that longer life is associated with healthier lives—adding life to years as the WHO put it. Second, the commitment to multi-disciplinarity is essential for ageing research because ageing is a complex life-long developmental process which requires understanding from many disciplinary perspectives. Third, the structural inequalities in ageing, both within and between countries, are a hugely

neglected aspect of gerontological research. Not so here because this volume highlights both inequality and heterogeneity. Fourth, there is a clear case made in this volume for the importance of policy and practice as the mechanisms essential to implement the results of research. If we are to improve health, cognition, and well-being as people age, we have to understand the processes by which research can be translated effectively into policy and practice.

It is with considerable admiration for the editors and other contributors, and with pride in their achievements as FLARE Fellows, that I wholeheartedly recommend this volume.

Sheffield, UK Alan Walker

Preface

This volume is proof of the success of long-lasting and major efforts to foster cross-national and cross-disciplinary ageing research in Europe. All first authors were funded or have been invited to take part in the framework of the European 3-year postdoctoral fellowship programme FLARE, Future Leaders of Ageing Research in Europe, coordinated by the European Research Area in Ageing (ERA-AGE), led by Prof. Alan Walker and his team at the University of Sheffield, UK. The main features of the FLARE programme are to promote both geographical and disciplinary mobility. Consequently, the contributions in this unique volume on health and cognition in old age are themselves the result of successful cross-national and cross-disciplinary collaboration and come from an international set of authors working at research institutions in Europe, Israel, and the USA at the postdoctoral level and above. This volume summarises the findings of their research programmes in various fields of ageing research, all relating to health, cognition, and well-being in old age, from various disciplines including biomedicine, general medicine, gerontology, geriatrics, immunology, psychology, epidemiology, public health, social policy, sociology, education, medical ethics, philosophy, and humanities. The volume comprises four parts: biomedical factors in ageing (Part I), life course factors constituting later-life health and cognition (Part II), care and interventions to maintain and improve impaired health, cognition, and well-being in old age (Part III), and policy and practice approaches for healthy and active ageing (Part IV). Taken together, the contributions provide a comprehensive overview of current developments in research on health and cognition in old age. Editing this volume on research findings originated under the FLARE scheme has been an amazing interdisciplinary journey for us and made us even more respectful of the multiplicity of perspectives in research on health and cognition in old age.

Walferdange, Luxembourg — Anja K. Leist
Jyväskylä, Finland — Jenni Kulmala
Vaasa, Finland — Fredrica Nyqvist

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First and foremost, we would like to acknowledge the work of Prof. Alan Walker and his European Research Area in Ageing (ERA-AGE) team at the University of Sheffield, UK, especially Juliet Craig. The ERA-AGE network has created a supporting structure at the European and national level in order to promote European ageing research. One of the main outcomes of ERA-AGE certainly is the development and realisation of the Future Leaders of Ageing Research in Europe (FLARE Joint Call) a postdoctoral fellowship programme promoting cross-national and multidisciplinary ageing research, to face the challenges of ageing societies. Two calls have been launched so far, in 2007 and 2010. Postdoctoral fellowships were funded by the member states themselves, and we are thankful to all countries that have participated in one or both calls. This volume hopefully is proof of timeliness, quality, and societal relevance of research funded under the FLARE scheme.

Sincere thanks goes to all members of the ERA-AGE consortium since 2005 and FLARE funding organisations, all of whom supported the FLARE program and its aims and ambitions:

- Austrian Academy of Sciences, Austria
- AGE Platform Europe, Brussels
- Institute of Population and Human Research at the Bulgarian Academy of Sciences, Bulgaria
- Canadian Institutes of Health Research, Institute of Aging, Canada
- Fonds de recherche du Québec—Santé, Canada
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- The Israeli Ministry of Health (CSO-MOH), Israel
- Istituto Superiore Di Sanità (ISS), Italy
- The Centre for Ageing Research and Development in Ireland (CARDI), Ireland

- The Latvian Council of Science (LCS), Latvia
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- University of Sheffield, UK (ERA-AGE Coordinator)

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The FLARE scheme has both extended the existing ERA-AGE network and created a professional network of young researchers across Europe in the field of ageing. On behalf of all FLARE participants, we would like to express our gratitude for the possibility to meet new colleagues and build new friendships. We are convinced that we will profit from this large and vibrant network throughout our research careers.

Special thanks also go to our mentors at the home and visiting institutions. All first authors of the contributions in this edited volume were funded or took part in the FLARE programme. These accomplishments would in most, if not all, cases not have been possible without consistent, helpful mentoring by former and current supervisors, senior researchers, and colleagues at the home and outgoing institutions. On behalf of the authors, we would like to thank all of them for sharing their expertise and time with us. We are deeply grateful to Juliet Craig and Miriam Buff for valuable help in reviewing the chapters.

We would also like to acknowledge the work of the expert reviewers of the contributions to this volume, who devoted their time and expertise to review and comment on the chapters. Considering the fact that the chapters span a wide range of topic from a variety of disciplines, these expert reviews ensure high quality of all contributions to this volume.

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Abbreviations

Abeta	Beta-amyloid
AD	Alzheimer's disease
AMPA	Alpha-amino-3-hydroxy-5-methylisoxazole-propionate
ApoE	Apolipoprotein E gene
ASC	Antibody-secreting cells
ASCOT	Adult social care outcome toolkit
BCR	B-cell receptors
BMI	Body mass index
CAIDE	Cardiovascular risk factors, aging and dementia
CDT	Clock drawing test
CHD	Coronary heart disease
CHIP	C terminus of Hsc70-interacting protein
CM	Case manager
CMV	Cytomegalovirus
CNSA	Caisse Nationale de Solidarité pour l'Autonomie
COR	Conservation of resources theory
CRP	C-reactive protein
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
DM	Diabetes mellitus
DR	Diabetic retinopathy
ECG	Electrocardiogram
ECM	Extracellular matrix
ED	Emergency department
EF	Executive function
ELSA	English Longitudinal Study of Ageing
EMCA	Ethnomethodological conversation analysis
ERA-AGE	European Research Area in Ageing
ESS	European Social Survey
FGF	Fibroblast growth factor
FIOH	Finnish Institute of Occupational Health

FLAME	Finnish Longitudinal Study on Municipal Employees
FLARE	Future Leaders of Ageing Research in Europe
FSG	Fasting serum glucose
FSR	Framingham stroke risk score
GEREC	Gerontology Research Center
HbA1c	Glycated haemoglobin
HIWP	High involvement work practices
HRQoL	Health-related quality of life
IGF-1	Insulin-like growth factor 1
IgH	Immunoglobulin heavy chains
IgL	Immunoglobulin light chains
IL-6Rα	Interleukin 6 receptor alpha
IRS-1	Insulin receptor substrate
LTC	Long-term care
MCI	Mild cognitive impairment
MetS	Metabolic syndrome
MMSE	Mini mental state examination
MTL	Medial temporal lobe
NMDA	*N*-methyl-d-aspartate
NOC	Nursing outcome classification
NPV	Negative predictive value
NRI	Net reclassification improvement
OECD	Organisation for Economic Cooperation and Development
PAMP	Pathogen-associated molecular patterns
PDGF	Platelets-derived growth factor
PET	Positron emission tomography
PI3K	Phosphatidyl-inositol-3 kinase
PI3-kinase	Phosphatidylinositide PI3-kinase
PON1	Paraoxonase 1
PPARγ	Peroxysome proliferators-activated receptor
PPV	Positive predictive value
QoL	Quality of life
RAND	RAND Corporation (Research ANd Development)
ROC AUC	Receiver operating characteristic curve
SCRQoL	Social care-related quality of life
SEP	Parental socioeconomic position
SHARE	Survey of Health, Ageing and Retirement in Europe
SHM	Somatic hypermutation
SOC	Theory of selection and optimization with compensation
SRF	Serum response factor
suPAR	Soluble urokinase plasminogen activator receptor
TGFβ	Transforming growth factor β
uPA	Urokinase type-plasminogen activator
uPAR	Urokinase plasminogen activator receptor
UPS	Ubiquitin proteasomal system

VaD	Vascular dementia
VISAT	Longitudinal Study VISAT (Vieillissement, Santé, Travail)
VSMC	Vascular smooth muscles
W/H	Waste/hip ratio
WAI	Work ability index
WHO	World Health Organization
WM	Working memory
αNTF	Alpha necrosis tumour factor
ε4	Isoform ε4

Chapter 1
Perspectives on Health and Cognition in Old Age: Why We Need Multidisciplinary Investigations

Anja K. Leist, Jenni Kulmala, and Fredrica Nyqvist

1.1 Definitions, Dimensions, and Determinants of Health and Cognition

Health in old age is a complex endeavor. Being and feeling healthy and well is the result of several complex processes, including both individual and environmental factors. Health is used here as overarching concept comprising a multitude of components such as physical functioning, cognitive health, mental well-being, self-regulation, and others. In the following, four perspectives on health and cognition in old age are outlined: the first perspective relates to biomedical aging, the second relates to life course influences on old age outcomes, the third to care and interventions for individuals with impaired health, and the fourth to policy and practice.

The first perspective on health and cognition in old age considers physiological bodily processes of the musculoskeletal, immune, cardiovascular, endocrine, and other systems that naturally have large impact on an older person's health and well-being. However, feeling healthy and well depends on several components which are insufficiently described by the absence of chronic diseases or physical disabilities. Individual resources, which will be dealt with throughout the volume, such as

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coping strategies and feelings of social integration and connectedness are also strong influences on well-being and health. A second perspective regards later-life cognition and health as a result of influences throughout the life course. In this sense, accumulated "advantages" or possibilities for positive development over the life course, through education, socioeconomic status, the workplace, social relationships, health behaviors, and other life course influences have substantial impact on health and cognition in old age. A third perspective on health and cognition in old age reflects the influences of the environment. Here, a favorable immediate social network and built environment are needed which meet and fulfill the needs and wishes of the older person. Since a considerable number of older adults are affected by functional limitations, chronic conditions or cognitive impairment, specific environments providing long-term care and related interventions have to be considered. Lastly, contextual factors at the national level have to be considered in studies on health and cognition in old age. Welfare policies concerning, for example, social and health care, pensions, insurance, and long-term care that meet financial, health, and social needs of the older person are considered key national determinants to promote a healthy and active old age. Thus, health and cognition are affected on several individual, environmental, and institutional dimensions, and it is thus necessary to investigate aging processes and outcomes from different perspectives and different disciplines.

When talking about health and cognition we have to acknowledge that these concepts are multifaceted and closely intertwined. Being and feeling healthy comprises many interrelated components, such as physical functioning, cognitive health, mental well-being, and self-regulation. Whereas some definitions of health propose subjective well-being to be a facet of the more general concept of health, others refer to psychological or subjective well-being as separate concept, which relates to subjective cognitive and affective evaluations of one's life (Diener 2000), and can be specified as self-acceptance, autonomy, personal growth, environmental mastery, and positive relations with others (Ryff 1989). New definitions of health suggest health to be "a dynamic state of well-being characterized by a physical and mental potential, which satisfies the demands of life commensurate with age, culture, and personal responsibility" (Bircher 2005, p. 336). Health is thus not an endpoint but a dynamic state, and health needs may change over the lifespan. Health may not even be "a state of complete physical, mental and social well-being" (World Health Organization 1958, p. 469). It may rather reflect potential for self-regulation, in particular "the ability to adapt and self-manage in the face of social, physical, and emotional challenges" (Huber et al. 2011, p. 1).

From this overview on the four dimensions, definitions, and determinants of health and cognition it becomes evident that these endeavors need a multidisciplinary perspective considering all presented dimensions and determinants. This volume aims to shed light on some of the current developments regarding the four dimensions, and, consequently, this contribution consists of four parts, related to: (1) biomedical factors, (2) the life course, (3) the environment, including care environments and interventions, and (4) policy and practice. Knowledge on how health and cognition in old age are influenced can be used, on the one hand, to prevent

physical, cognitive, and emotional impairments for as long as possible, and, on the other hand, to promote cognition, health, and well-being of persons living with chronic conditions and disabilities.

1.2 The Motivation for Investigations on Health and Cognition in Old Age

Health in old age matters for several reasons. First, it is a human right that every individual, no matter what age and health status, should be given the possibility to live and feel well. Saracci (1997) defines health as "a condition of well-being, free of disease or infirmity, and a basic and universal human right" (p. 1410). Although this postulate rightfully refers to health as a universal right, it may be harder to meet in older age, when aging-related bodily changes lead to impairments and chronic conditions by which a considerable part of the aging population is affected. Striving for the best health possible in individuals of all ages is especially important as people are living longer, and a large number of older people live with impaired physical or cognitive functioning and may need help and support to maintain or improve their health, well-being, and ensure their dignity. Second, the time lived in older and old age is proportionally increasing due to longer life expectancy and improved health care. Although the total life expectancy has been increasing, more attention should still be paid to *healthy life expectancy*, denoting the time lived in good health, which is considerably shorter than, and has not increased proportionally with, life expectancy (Jagger et al. 2008; Jagger et al. 2013). Ensuring that improvements in medical treatment do not only lead to prolonged but also healthier and happier lives should be at the top of the gerontological research agenda. Third, an important argument for investigating health and cognition in old age targets society: in addition to increasing life expectancy, decreasing fertility in Western societies has led to the necessity to place older persons' needs on the agenda by adjusting welfare provisions such as social and health care and financial support (e.g., pensions) to correspond to the needs of the older population. And, rather than evaluating population aging as an economic and welfare burden, it is necessary to acknowledge that older people heavily contribute to society by giving care to children and adults in need, by volunteering, financial transfers within families, and through many other activities. Consequently, this demographic shift calls for a more positive approach to aging and older people than is currently the case (Walker and Maltby 2012). We should consider new ways how older adults, despite no longer belonging to the work force, can stay active members of society and contribute to the functioning of society in various domains such as (grandparental) childcare, care of others (e.g., caregiving for kin), paid or volunteer work, and other activities.

Another motivation to investigate health and cognition in old age is to explain and reduce social inequalities. There is a large variation in health in old age according to educational attainment and socioeconomic status, with less affluent individuals bearing greater risk of impaired cognition, health, and well-being compared with

more affluent individuals. These social inequalities in older age are not unique to developed societies and have, in the last decades, rightfully received rising attention in public discussions and policy making all over the world. Social inequalities are again the result of influences on several dimensions. First, they result from physiological processes that render individuals more or less prone to disease and disability and may determine, to some extent, further possibilities for positive development through education, career pathways or social relationships. Further, social inequalities result from a life course accumulation of advantages and disadvantages, such as the confrontation with positive and negative life events or access to jobs with more or less potential to engage in cognitively stimulating activities, which may relate to later-life health and other outcomes. Another important role is played by the immediate social and built environment such as exposure to pollution, crime, and other hazards, as well as policy issues, such as more or less equal access to education, health care, or social welfare. Life course theory suggests that throughout the lifespan these advantages and disadvantages cumulate, meaning that singular disadvantages at earlier life stages may lead to further deprivation at later life stages, may spill over from one life domain to the other, and thus widen the gap between more and less advantaged individuals over time (cf. Dannefer 2003). The outcome of these processes of cumulative advantages and disadvantages over the life course can certainly not be overestimated: never throughout their lifespan are individuals more heterogeneous as in older age. Educational attainment, occupational, and other skills related to, e.g., health literacy and health management, as well as chronic conditions, cognitive function such as executive function and memory, social network, rural or urban living environment, and types and range of coverage of welfare regimes make individuals in old age a heterogeneous group, for which, consequently, no general conclusions can be drawn. Feeling healthy and well is easily maintained for many older individuals, but for others reachable only partly and after large effort. Nonetheless, the contributions in this volume aim at bringing forward knowledge on explaining these differences in health and cognition in old age, and through this knowledge targets for interventions aiming at promoting a healthy and active old age can be obtained.

1.3 The Current Volume

This volume aims at providing an overview of current developments in research on health and cognition in old age, approaching this topic from the biomedical (Part I), life course (Part II), care and interventions (Part III), and policy and practice perspective (Part IV).

Part I presents five current projects investigating biomedical processes in the aging person, both through original research and through evaluations of implicit and explicit conceptions of "aging" in this field. The chapter by *Kiyan* et al. deals with new evidence on the role of the urokinase system in vascular aging. *Herghelegiu* and *Prada* are concerned with the relationship between diabetes and cognitive function in

older age and, by reporting original research, illustrate the importance of metabolic control in maintaining cognitive function in older adults with diabetes. *Shahaf* and colleagues summarize their research on immune systems cell development and antibody repertoire in aging organisms. *Herndler-Brandstetter* builds and extends on original research on the aging immune system and proposes consequences and perspectives for interventions. The chapter by *Ehni* closes the biomedical section with ethical aspects of applying biogerontology to medicine and critically discusses biogerontological and social gerontological conceptions of aging and old age.

Part II is comprised of reviews on how early and midlife social and behavioral factors influence later-life outcomes, with a strong focus on physical and cognitive functioning. *Kulmala* and *M.B. von Bonsdorff* provide an overview of work-related determinants of old age health and physical functioning. *Leist* and *Mackenbach* review findings on social, behavioral, and contextual influences on cognitive function and its decline over the life course. The chapter by *Dahl Aslan* deals with the relationship between obesity, life course weight histories, and cognitive function and dementia, with a particular focus on the shifting associations between obesity and cognitive function between mid-adulthood and older age. Extending on these chapters on life course influences on later-life cognitive function, *Stephan* gives an overview of current approaches to predicting risk of dementia by lifestyle, neurological, and other factors and points to the methodological challenges of this endeavor. The chapter by *Qiu* closes the third part with a detailed review on the importance of lifestyle factors in the prevention of dementia.

Part III discusses perspectives on care and interventions which serve as examples of environmental influences in maintaining and improving health and cognition in old age. It consists of three papers focusing on different aspects of formal and informal care of older people, and one paper describing interventions aiming at improving cognitive functioning in old age. *Trukeschitz* critically reflects different approaches of measuring quality of long-term care. She discusses the theories, concepts, and methodological challenges related to quality in the long-term care of older people. *Meidani* describes family configurations and cultural aspects associated with care of dementia patients. She also evaluates the rationalities and strategies of care givers in both formal and informal sectors. *Hasson* and *Topo* systematically evaluate implementation processes of improvement programs in older people care. They aim at providing further understanding of employees' participation in the improvement programs and describe how different factors influence the implementation. *Grönholm-Nyman* describes how executive functions can be trained in healthy older adults and in persons with mild cognitive impairment.

Part IV covers active and healthy aging from a policy and practice perspective, focusing on inclusion and participation of older people. The chapters in this section examine resources for participation and inclusion at different life stages from an individual as well as policy perspective. The chapter by *Isopahkala-Bouret* explores the relationship between adult education and active aging by analyzing interviews with graduates who have acquired a master's degree in their 50s. *Rauniomaa*, *Laurier,* and *Summala* deal with age-related challenges older drivers may face as they drive in real traffic situations. *M.E. von Bonsdorff* and

M.B. von Bonsdorff summarize retirement and late-career research with a special focus on the role of individual resource allocation strategies and human resource management in promoting the work ability of older employees. The chapter by *Nyqvist* and *Cattan* presents the concepts of social capital and mental well-being and discusses the meaning of social capital for mental well-being in terms of absence of loneliness in older people. The last chapter by *Komp* discusses social policies for older people and focuses on the impact of shifting images of old age and of time lag in policy making.

Many of the contributions are the result of tremendous and unique research efforts during the last decades to design population-representative surveys and to harmonize datasets in order to allow for cross-national comparisons as well as cross-disciplinary collaboration. At the same time, small-scale studies with qualitative approaches and utilizing experiences of older people have also gained valuable knowledge on important aging phenomena. By combining high quality quantitative and qualitative studies, a more comprehensive picture of aging can be achieved. Consequently, the contributions in this volume come from several disciplines, including biomedicine, general medicine, gerontology, geriatrics, immunology, psychology, epidemiology, public health, social sciences, sociology, medical ethics, philosophy, and humanities. It is highly desirable that future research efforts will continue this successful mix of methods, data, and cross-disciplinary collaboration in order to find new innovative ways of gaining evidence about unresolved research questions.

This volume can only capture a few of the pressing topics in current aging research. Technological innovations for older adults, the keywords being ambient assisted living, telehealth, telemedicine, ICT-supported housing and care, remain to be addressed in other volumes. Research on housing and neighborhood architecture for aging individuals, as well as city and traffic planning for an aging society are also desiderata to be addressed in other contributions.

The contributions of this volume remain to be evaluated: how can research presented here be used to design interventions to improve later-life health in the field? When describing interventions, the concept of *social innovation*, i.e., an innovation with a social purpose, can be used to translate evidence on health and cognition in old age into implementation strategies for interventions with the aim of maintaining or even improving the health of older people. Contexts are manifold and span from interventions at the individual (micro) level (e.g., at home, the workplace), at the neighborhood or community (meso) level (e.g., residential areas, hospitals, residential care), and at the national (macro) level. Innovations with the aim of improving health in old age can target the whole life course, by lifelong learning, dietary and physical activity interventions, building and strengthening social ties, and again, by modifying and adjusting the built environment. Last but not least, reflections are necessary on ethical challenges accompanying aging research. It is highly possible that policymakers, researchers, and the "users," i.e., the older person, have to some extent diverging perspectives on, for instance, explicit and implicit definitions of a good life in old age, rights and duties of the older individual, or end-of-life decisions. Discussions and reflections on these different perspectives are essentially needed to accompany research on a healthy and active old age.

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Part I
What Constitutes Health, Cognition, and Well-Being in Old Age from a Biomedical Perspective?

Chapter 2
Vascular Aging: Revealing the Role and Clinical Perspectives of the Urokinase System

Yulia Kiyan, Bianca Fuhrman, Hermann Haller, and Inna Dumler

The average lifespan of humans is growing gradually, resulting in an increased percentage of people entering the 65 and older age group. It is expected that this age group will reach 20 % of the population by 2030. It is also predicted that more than 40 % of all deaths in this age group will result from cardiovascular diseases (CVD). Therapy costs will triple by 2030 (Heidenreich et al. 2011). Age is the most important determinant of vascular health. Conversely, a healthy cardiovascular system is of vital importance for an organism's longevity. More than 100 years ago, Sir William Osler (1849–1919) formulated accordingly: "You are as old as your arteries." Indeed, arterial health remains a valid predictor of disease risk and all-cause mortality. Understanding the nature and molecular mechanisms of age-related vascular dysfunction and its relation to CVD constitutes an important task for biomedical research aiming at developing new therapeutic strategies and improving the quality of life of the elderly population.

In this chapter, we will review the progress achieved in research deciphering the molecular mechanisms of vascular aging, address general and vascular disease-related functions of the urokinase-type plasminogen activator (uPA)/uPA receptor (uPAR) system, and finally give a short overview of therapeutic strategies being developed to target the urokinase system.

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2.1 Aging and Cardiovascular Diseases

Independently of other risk factors like hypertension, diabetes, and hypercholesterolemia, aging results in progressive morphological and functional changes in the vascular wall. The arterial wall is comprised of three layers: *tunica intima*, a single layer of endothelial cells lining the interior surface of the blood vessels; *tunica media*, circularly arranged vascular smooth muscle cells (VSMCs) embedded in VSMC-produced extracellular matrix (ECM), maintaining vascular tone; and *tunica adventitia*, connective tissue containing predominantly fibroblasts. Aging is characterized by changes in endothelium and VSMCs, leading to arterial wall thickening and increased stiffness along with exaggerated expression of inflammatory molecules and elevated uptake of plasma lipoproteins. These changes are clinically manifested by increased systolic pressure and represent a major risk factor for developing atherosclerosis, hypertension and stroke, and arterial fibrillation (North and Sinclair 2012).

Important functions of the endothelium include controlling vascular contraction/dilation, barrier function, and controlling blood clotting and inflammation. All of these change during aging. Endothelial dysfunction is considered as one of the main mechanisms of age-associated development of CVD. The hallmark of aged endothelium is diminished endothelium-dependent vessel vasodilatation. The availability of nitric oxide, the main endothelium-derived vasodilator, progressively decreases with age, whereas release of vasoconstriction factors increases along with secretion of pro-inflammatory molecules and enhancement of oxidative stress (El Assar et al. 2012).

Both endothelial cells and VSMCs are mitotic cells (Box 2.1) demonstrating proliferative response to injury to promote tissue repair. Mitotic cells having critically

Box 2.1 Mitotic and Postmitotic Cells

According to the classical view, cells of multicellular organisms are classified as terminally differentiated postmitotic cells, which cannot reenter the cell cycle and divide, and mitotic cells capable of proliferation. Depending on the proliferative capacity of the tissues, multicellular organisms are termed as simple or complex. After the development of the organism is completed, all non-germ cells of simple organisms (such as *Caenorhabditis elegans* and *Drosophila melanogaster*) are terminally differentiated postmitotic cells. Complex organisms such as mammals are composed of both postmitotic and mitotic cells. Mitotic cells are present in renewable tissues such as the skin, intestines, liver, kidney, and blood vessel wall, and enable renewal and repair. In addition, mitotic cells include the undifferentiated stem and progenitor cell populations.

The ability of a tissue to renew and repair allows complex organisms to achieve a significantly longer lifespan compared with simple organisms. However, mitotic cells are susceptible to malignant transformation and may undergo cellular senescence when challenged with carcinogenic genotoxic stimuli.

shortened telomeres because of replication exhaustion or challenged with extrinsic or intrinsic genotoxic stress may undergo cellular senescence—irreversible growth arrest. Senescent cells, however, remain metabolically active, show altered resistance to cell death (apoptosis) signals, and acquire a pro-inflammatory gene expression profile. Induction of cellular senescence is the main tumor-suppressor mechanism, which stops proliferation of incipient cancer cells. However, in aging organisms, senescence deteriorates tissue regeneration and repair, and promotes inflammation (Campisi and d'Adda di Fagagna 2007). This forms the main concept of the antagonistic pleiotropy hypothesis, first proposed by George C. Williams (1957) as an evolutionary explanation for aging. Senescent endothelial cells demonstrate decreased response to vascular injury. The integrity of the endothelial barrier becomes impaired, which in turn facilitates recruitment of inflammatory cells from the bloodstream and leads to VSMCs activation, migration, and proliferation (Wang and Bennett 2012). Extensive evidence also documents the presence of senescent VSMCs in aged vessel walls and within atherosclerotic plaques (Mahmoudi et al. 2008).

VSMCs comprise the medial layer of the blood vessel wall, and fulfill a variety of structural and physiological functions. During development, VSMCs produce ECM that gives the arterial wall the capacity to endure the pressure of circulating blood. Physiologically, the contractile activity of VSMCs generates blood pressure and regulates the vascular tone in response to mechanical and soluble factors. These cells express specialized compositions of contractile proteins, ion channels, and signaling molecules. This repertoire is unique in comparison to other cell lineages and serves as a marker of differentiated VSMCs. VSMCs are intrinsically involved in age-associated changes in the vasculature. With age VSMCs change from the physiological contractile phenotype, characterized by contractile activity maintaining vascular tone, towards the pathophysiological synthetic phenotype. Synthetic VSMCs are characterized by migration, proliferation, and release of inflammatory cytokines, as well as ECM synthesis. Progressive VSMC migration from the tunica media results in intima thickening, which leads to blood vessel lumen narrowing and creates a site of increased susceptibility to atherogenic factors even of low grade (Lacolley et al. 2012).

Various external and intrinsic transcriptional regulatory pathways cooperate to promote age-associated VSMC phenotypic changes. The balance between growth-promoting cytokines and growth factors [such as platelet-derived growth factor (PDGF), thrombin, fibroblast growth factor (FGF), and interleukin-1] and growth inhibitors/inducers of differentiation [such as transforming growth factor beta (TGFβ)] defines the transcriptional activity and the actual phenotype of VSMCs. One important transcription factor that dually regulates the VSMC phenotype is the serum response factor (SRF). Promoter-enhancer regions of most VSMC contractile genes contain multiple CArG and a TGFβ control element. Binding of SRF in complex with its main VSMC lineage cofactor myocardin (Box 2.2) to the CArG box activates the expression of contractile genes (Chen et al. 2002). On the contrary, when dissociated from myocardin and bound to the ETS domain-containing transcription factor, Elk-1, SRF activates the expression of immediate early genes and induces proliferation of VSMCs. In addition, as reviewed by Zheng et al. (2010), some reports, though contradictory, have shown the role of Kruppel-like factor 4 transcription factor in

Box 2.2 Myocardin Transcription Coactivator

Myocardin protein, recently discovered by Eric Olson's group (Wang et al. 2001), is a transcriptional coactivator of genes encoding smooth muscle-specific cytoskeletal and contractile proteins. Myocardin is the founding member of a protein family that includes myocardin itself and the two myocardin-related transcription factors, MRTF A and B. All of them show similar multi-domain organization that provides putative binding sites for several transcription factors and actin. The most important is the ternary complex that myocardin and MRTFs form with the MADS-box transcription factor, SRF, to synergistically activate transcription of contractile proteins. Vascular injury and other stimuli ultimately target myocardin/SRF complexes to modulate the VSMC phenotype.

Forced expression of myocardin in embryonic stem cells induces the expression of multiple contractile genes including SM-22α, SM-MHC, and SM-α-actin. Mice harboring a null mutation in the myocardin gene survive only to embryonic day (E)10.5 and exhibit obvious defects in the vasculature, including inhibition of smooth muscle cell differentiation. These data demonstrate that myocardin promotes VSMC differentiation and the contractile phenotype.

phenotypic modulation of VSMCs. Transcription pathways of age-dependent VSMC proliferation are also related to endothelial dysfunction. For example, diminished Jagged1 expression in aged endothelium has been shown to enhance VSMC proliferation and neointima formation after arterial injury (Wu et al. 2008).

In addition to growth factors, modified (phospho-) lipids and plasma lipoproteins are important factors regulating VSMC phenotypic modulation. Similar to PDGF-BB, oxidized phospholipids induce Elk-1 phosphorylation and binding to SRF, which results in inhibition of contractile genes' expression (Pidkovka et al. 2007; Yoshida et al. 2008). Outward radial convection of plasma lipoproteins and their retention by VSMC-secreted sulfated proteoglycans have also been shown to induce VSMC phenotypic modulation towards the synthetic and proliferative phenotype (Karagiannis et al. 2013; Padro et al. 2008). MicroRNA (miRNA) and reactive oxygen species (ROS) are also important regulators of the VSMC phenotype, affecting gene transcription, DNA damage, and expression of inflammatory genes (Davis-Dusenbery et al. 2011; Antoniades et al. 2009; Heistad et al. 2009).

Despite the progress achieved in VSMC physiology research, their significance in aging and vascular pathology remains to a high degree underestimated. The main role in initiation and progression of aging-associated diseases like atherosclerosis is attributed to inflammatory and endothelial cells. Some controversies still exist, and clear understanding of the underlying molecular mechanisms of VSMC phenotype regulation and senescence is far from being achieved. Recent reports, however, brought more attention to the functions and fate of VSMCs during atherogenesis. They also shed some light on a very complicated and controversial matter of lineage

tracing of particular cells within the plaque (Gomez and Owens 2012; Rong et al. 2003). In the early stage of plaque development, low-density lipoproteins (LDL) become trapped in the intima because of binding of apolipoprotein B100, the protein component of the LDL particles, to proteoglycans produced by VSMCs. Trapped lipoproteins are being modified and taken up at an enhanced rate by macrophages, resulting in the formation of macrophage foam cells, which contribute to the progression towards a more complicated lesion. More advanced atherosclerotic plaque includes migrated VSMCs, producing excessive ECM, and inflammatory cells such as macrophages, T lymphocytes, dendritic cells, and mast cells. Macrophage-derived foam cells eventually die by apoptosis, releasing their content into the plaque and further amplifying inflammation. Extracellularly located lipids and cell debris comprise a necrotic core surrounded by a fibrous cap of VSMCs, critically influencing the plaque's stability. VSMC death and degradation promote plaque rupture and may lead to thrombosis. Increased VSMC content has long been associated with plaque stability, and VSMC proliferation and ECM synthesis may promote plaque repair. Advanced plaques show multiple sites of plaque rupture and repair that ultimately lead, however, to vessel narrowing.

A recent report has shown that the role of VSMCs is not limited to structural maintenance of the plaques. VSMCs show active endocytic and phagocytic activities. They take up modified lipoproteins, and foam-like cells originating from VSMCs have been reported. In addition to lipoprotein uptake, VSMCs may engulf by phagocytosis apoptotic cells, crystals, and microparticles (Lacolley et al. 2012). VSMCs also propagate the inflammatory response by various mechanisms (Cole et al. 2010; Krug et al. 2010; Orr et al. 2010). Calcification of VSMCs leads to further arterial stiffness and clinical complications (Ellam and Chico 2012). Furthermore, essentially all these processes are influenced by VSMC senescence. Importantly, different activities of VSMCs induce expression of different markers that are not intrinsically expressed in VSMCs. Thus, endocytic activity endows VSMCs with expression of phagocytic markers like CD68 (Rong et al. 2003). On the contrary, cells other than the VSMC lineage express markers like smooth muscle α-actin, which is typically used to detect VSMCs (Gomez and Owens 2012). To summarize, recent reports have suggested that the role of VSMCs in aging and atherosclerosis is largely underestimated. Multiple mechanisms and signaling pathways define the phenotype and functional response of VSMCs. Deeper understanding of VSMC functions and regulation is important for developing effective therapeutic approaches.

2.2 uPA/uPAR System

Recent studies have revealed a profound interconnection between the fibrinolytic system, namely, the serine protease uPA and its specific multifunctional receptor (uPAR; Box 2.3), and the pathogenesis of CDV, inflammation, aging, and mortality. As reviewed by Binder et al. (2007), significant insight into the molecular basis of how uPA-/uPAR-directed cell behavior affects the pathogenesis of CVD has been gained.

Box 2.3 The uPA/uPAR Plasminogen Activator System

The serine protease uPA is the most effective physiological activator of plasminogen. uPA converts inactive proenzyme plasminogen to the active serine protease plasmin that in turn degrades fibrin polymers of blood clots into soluble degradation products.

Binding of uPA to its receptor (uPAR) enhances activation of pro-uPA into its active form, resulting in activation of plasminogen. uPAR is associated with the external surface of the cell plasma membrane by a glycosylphosphatidylinositol (GPI) anchor. Because uPA binds to uPAR and plasmin binds to multiple cellular receptors, the proteolysis is concentrated at the cell surface. In addition to fibrin, plasmin cleaves a broad spectrum of substrates. Plasminogen activators are involved in a wide range of physiological and pathophysiological processes associated with basement membrane and ECM turnover, for example, tissue remodeling and repair, tumor progression, and metastasis.

uPAR is a cell-surface GPI-anchored protein that can be shed from the cell membrane in a soluble form. Recent large-scale population studies identified soluble uPAR (suPAR) as a new independent inflammatory marker associated with the risk of CVD (Lyngbaek et al. 2012). These studies have shown that the circulating suPAR level is associated with subclinical organ damage, manifested as carotid atherosclerotic plaques, and thus may be even better for prediction of future CVD than the "classical" C-reactive protein (CRP) level, which mainly reflects inflammation associated with metabolic disturbances. uPAR expression in tissues is low under normal conditions. However, uPA/uPAR is drastically upregulated in numerous diseases, primarily those related to inflammation, vascular remodeling, and cancer (Binder et al. 2007; Pillay et al. 2006; Blasi and Carmeliet 2002).

Binding of uPA to its receptor is implicated in plasmin generation and extracellular proteolysis. In addition, the uPA/uPAR system also has a nonproteolytic role and induces various intracellular signaling pathways. Thus, uPAR realizes two important cellular functions: providing regulation of extracellular proteolytic cascades and serving as a signaling receptor to promote changes in cell functional behavior (Smith and Marshall 2010). uPAR-directed signaling can occur via uPA–uPAR binding or be uPA independent. As a GPI-anchored receptor lacking transmembrane and intracellular domains, uPAR associates with transmembrane proteins, such as integrins, tyrosine kinase receptors, and others, to initiate signal transduction. Multiple signaling cascades induced via these co-receptor cooperation have been identified over the last decade (Smith and Marshall 2010; Blasi and Carmeliet 2002). Although many advances have been made in the field, the mechanisms of uPAR signaling are still not completely clear and several controversies remain. At the level of cellular functions determining the cell fate in response to the microenvironment, uPAR-directed signaling is believed to regulate physiological and pathophysiological conditions, requiring changes in cell proliferation, migration, adhesion, and survival (Pillay et al. 2006). Because of these multifunctional properties, uPAR presents many opportunities to be used as a target for specific therapies in diverse human diseases.

2.3 uPAR in Vascular Diseases and Aging

Several reports have documented the presence of senescent VSMCs in the aging vessel wall and in atherosclerotic plaques. Senescent cells, though growth arrested, remain metabolically active and secrete multiple factors that may affect surrounding cells. Generally, the senescence-associated secretory phenotype (SASP), or the senescence-messaging secretome, promotes inflammation. Recently, large-scale analysis of SASP has been performed by Campisi and colleagues (Coppe et al. 2010). Three major families of factors are secreted by senescent cells, including soluble signaling factors (interleukins, chemokines, and growth factors), insoluble proteins/ECM components, and secreted proteases. The proteases include matrix metalloproteinases (MMPs), serine proteases, and regulators of plasminogen activation, including uPA and uPAR. Upregulated expression of the system has also been well documented in vascular remodeling and atherosclerosis (Binder et al. 2007). The main stream of research on the role of uPA/uPAR in vascular pathology is focused, however, on the expression and function of this system in adhesion/migration of inflammatory cells. In our research, we have identified several novel links between the urokinase system and the functional behavior of VSMCs during vascular remodeling and initiation/progression of atherosclerosis.

Over a decade ago, it has been reported by our group and others that uPA induces migration and proliferation of VSMCs (Dumler et al. 1998). As a GPI-anchored protein, uPAR needs to be associated with other transmembrane receptors to induce intracellular signaling. In our studies, we have identified PDGF receptor beta (PDGFR β) as a uPAR co-receptor in VSMCs (Kiyan et al. 2005). We have shown that uPA-activated uPAR associates with PDGFR β and induces phosphorylation and dimerization of the latter in the absence of its natural ligand PDGF, the main regulator of VSMC migration and proliferation. Phosphorylation of tyrosine residues in the PDGFR β cytoplasmic domain provides sites for interaction with multiple downstream signaling proteins. Furthermore, we have shown that uPA-/uPAR-induced activation of phosphatidylinositide 3-kinase (PI3K) and Rho proteins in VSMCs is mediated by their interactions with PDGFR β (Kiian et al. 2003; Kiyan et al. 2005).

Because uPAR/PDGFR β induces a VSMC proliferative and migratory response that requires phenotypic modulation of VSMCs, we have examined if and how uPAR interferes with the transcriptional activity of VSMCs and the expression of contractile proteins. We observed that uPAR expression correlates with the VSMC synthetic phenotype and that downregulation of uPAR by siRNA not only abolishes uPA-dependent events but also promotes VSMC differentiation towards the contractile phenotype (Kiyan et al. 2009). These observations correspond with in vivo and clinical data, showing increased expression of uPA/uPAR at sites of vascular remodeling and atherosclerosis, which contain phenotypically modulated VSMCs. Moreover, we have investigated the molecular mechanisms of VSMC phenotypic modulation in response to uPA. As mentioned above, most smooth muscle-specific genes characterizing the contractile phenotype contain common CArG elements in their promoter region. Binding of SRF in cooperation with the cofactor, myocardin, to these elements regulates expression of the corresponding genes. Using chromatin immunoprecipitation, we have shown that SRF/myocardin binding to promoters of contractile genes is

Box 2.4 The Ubiquitin Proteasome System

The ubiquitin proteasome system (UPS) includes ubiquitin ligation enzymes and proteasome particles. It is the major non-lysosomal pathway of protein degradation in eukaryotic cells. Nearly every cellular process is affected by the UPS. It performs regulatory functions by eliminating no-longer-needed proteins and quality control functions by degrading misfolded or damaged proteins.

Protein degradation by UPS is ATP dependent and a substrate-selective process. Substrate proteins are typically modified by energy-dependent covalent attachment of the small protein ubiquitin polymers via concerted action of ubiquitin ligation enzymes.

The 26S proteasome comprises two subcomplexes: the proteolytically active 20S core particle (CP) and the 19S regulatory particle. The latter is responsible for substrate recognition, removal of substrate polyubiquitin, unfolding, and translocation into the CP for degradation.

suppressed by uPA/uPAR signaling (Kiyan et al. 2012). Furthermore, myocardin is modified by ubiquitination, and the protein level of myocardin decreases after VSMC treatment with uPA, because of proteasomal degradation (Box 2.4).

The pathway includes internalization of membrane uPAR via the pinocytic amiloride-sensitive pathway and its nuclear translocation. In the cell nucleus, uPAR interacts directly with myocardin to induce its dissociation from SRF, resulting in decreased expression of contractile genes. Furthermore, myocardin translocates to proteasome-containing nuclear structures and undergoes degradation. Our experiments with expression of truncated forms of myocardin demonstrated that its N-terminal domain is required for binding uPAR. Thus, our new observations have shown that uPAR serves as a myocardin cofactor and directly interferes with the regulation of gene expression in VSMCs. Interestingly, nuclear localization and transcriptional activity of uPAR have also been reported in cancer cells (Asuthkar et al. 2012). uPA/uPAR provides a relatively rapid pathway for VSMC phenotypic modulation, because of myocardin degradation. In our study, we did not identify the nature of the enzyme conducting the myocardin ubiquitination. Recent evidence (Xie et al. 2009) has shown that the E3 ligase C-terminus of Hsc70-interacting protein (CHIP) ubiquitinates myocardin and represses myocardin-dependent gene expression and transcriptional activity.

Another interesting observation from our study was the intersection of the uPA/uPAR system and the UPS. The proteasomal system is the main pathway of protein degradation in eukaryotic cells. It is absolutely essential for maintaining cellular homeostasis by degrading damaged and dysfunctional proteins. Furthermore, the proteasome has an important regulatory function in events such as regulation of transcription, cell cycle, DNA repair, and apoptosis. In addition, inflammation and

regulation of oxidative stress are tightly controlled by the UPS. The system includes enzymes performing protein ubiquitination/deubiquitination and a 26S multisubunit proteasome complex that exerts proteolytic functions. A concerted action of E1, E2, and E3 ubiquitinating enzymes results in activation and conjugation of ubiquitin to a target protein. Protein ubiquitination determines if modified proteins undergo degradation via the 26S proteasome particle. Alternatively, ubiquitination may lead to protein functional alterations and/or regulate its intracellular localization. Inhibition of the proteasome leads to accumulation of misfolded and damaged proteins, and may result in cell death. In addition, the proteasome is essential for repairing DNA damage and cell cycle regulation. These features make the proteasome system an attractive target for developing anticancer therapy. Aging and senescence are generally associated with decreased proteasomal degradation and accumulation of dysfunctional proteins. Scientific progress made in recent years also confirmed the role of the UPS in atherosclerosis. In particular, the proteasome is implicated in promoting endothelial dysfunction, an initial stage of the disease (Herrmann et al. 2010). In advanced plaques, accumulation of ubiquitin conjugates and its correlation with apoptotic cell death suggests that proteasomal degradation is decreased. In uPAR-knockout mice, i.e., genetically engineered mice lacking expression of uPAR, we have observed that the proteasomal activity in aortic tissue is lower than that in wild-type mice (Kiyan et al. 2012). Thus, impaired proteasomal degradation of myocardin may explain the delayed vascular remodeling after injury, which we have shown in uPAR-knockout mice using the carotid artery ligation model.

In an attempt to explore additional relationships between uPAR and the UPS, we used a model of doxorubicin (Dox)-induced cell senescence. Senescence of mitotic cells may result from critical telomere shortening at the chromosome ends, because of replicative exhaustion, and is called “replicative” senescence. Alternatively, various genotoxic agents may cause the so-called “stress-induced premature” senescence. Multiple mechanisms are involved in cell senescence in aging and atherosclerosis. Moreover, they probably have cumulative effects on each cell type. Thus, both aged and plaque VSMCs and endothelial cells demonstrate telomere shortening. Additionally, oxidative stress may promote senescence by various mechanisms; epigenetic modifications have been shown not only as markers of senescence but also as playing a causative role. It has been reported recently that proteasome function is important for developing Dox-induced senescence in cardiomyocytes (Maejima et al. 2008). Dox is an anthracycline antibiotic, proven to be effective for cancer treatment. However, its application is strongly limited by severe cardiac toxicity. Recent research has shown that the mechanism underlying Dox toxicity involves induction of cellular senescence. We have tested the Dox effect on VSMCs and observed that Dox also induces senescence of VSMCs (Hodjat et al. 2013). VSMC treatment with Dox was accompanied by a boost of proteasome activity, most probably induced by DNA damage response mechanisms, which later resulted in cell senescence. Interestingly, uPAR-deficient cells failed to upregulate the proteasome activity and were protected against developing senescence. Among the proteins degraded by the proteasome in response to Dox is the telomere-binding factor-2 (TRF-2)—a component of the shelterin protein complex, protecting

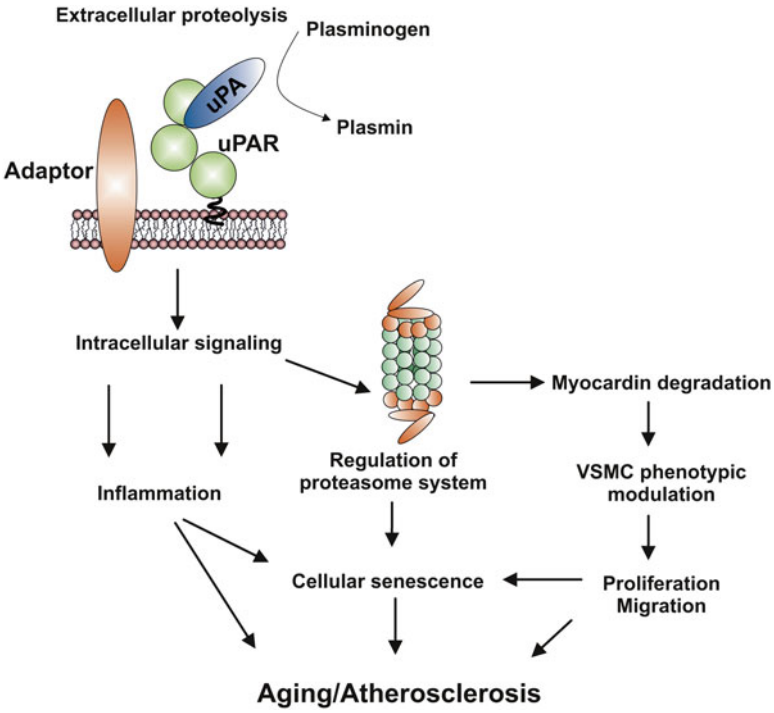

Fig. 2.1 The uPA/uPAR system regulates the physiology of VSMCs. In addition to mediating extracellular proteolysis, uPA/uPAR induces intracellular signaling that regulates the proteasome system. uPAR-regulated proteasome activity degrades myocardin and induces phenotypic modulation of VSMCs towards the synthetic state, accounting for protein turnover leading to cellular senescence

telomeres from being recognized as DNA breaks, leading to activation of the DNA damage pathway and cell cycle arrest. Proteasome degradation of TRF-2 was also impaired in the absence of uPAR.

Taken together, our data point to a new function of uPAR, which is directed at regulation of the proteasome system (Fig. 2.1). This may have crucial effects on cell physiology and survival. In acute response, uPAR serves as a myocardin cofactor, inhibiting its interaction with SRF, thus decreasing the expression of contractile genes. Absence of uPAR abolishes myocardin proteasomal degradation. In Dox-induced VSMC senescence, uPAR is essential for stress-induced activation of proteasomal activity and promotes degradation of TRF-2. Overall, the uPA/uPAR system seems to promote VSMC differentiation to the synthetic phenotype and plays deleterious roles in the progression of vascular diseases.

uPA has also been shown to promote oxidative stress in VSMCs and macrophages. Fuhrman and colleagues have shown that uPA activates the NADPH oxidase complex in macrophages, resulting in ROS production (Fuhrman et al. 2008). Our recent study defined an additional pathway of oxidative stress regulation by

uPA/uPAR. Paraoxonase 1 (PON1), a high-density lipoprotein (HDL)-associated lipolactonase, is the most studied member of the closely related PON family. Epidemiological and clinical studies unraveled a protective role of PON1 in atherosclerosis, but the mechanisms are just beginning to be understood. Studies performed on PON1-knockout mice have shown significant changes in the arterial wall, including increased oxidative stress, thrombogenicity, and increased leukocyte adhesion. HDL-associated PON1 regulates macrophage differentiation and has antioxidative and anti-inflammatory functions (Aharoni et al. 2013). PON1 is synthesized and released into the circulation by liver cells. Our study has shown that uPA/uPAR may regulate the expression of PON1 in the liver and thereby the availability of PON1 in the blood. Moreover, uPAR-dependent signaling relies on nuclear export of peroxisome proliferator-activated receptor γ (PPARγ) (Khateeb et al. 2012).

Thus, the urokinase system exerts its functions at different levels. It may regulate liver production of PON1, which is known to decrease oxidative stress in atherosclerotic lesions and attenuate the development of atherosclerosis. Furthermore, our research has shown that the urokinase system regulates VSMC modulation towards the synthetic phenotype, resulting in increased vascular remodeling and progression of atherosclerosis. uPA/uPAR induces a phenotypic modulation of VSMCs via proteasomal degradation of the transcription factor, myocardin, leading to increased migration and proliferation of VSMCs. The urokinase system's interference with the proteasomal system also has crucial importance for the induction of VSMC senescence, which may additionally influence the outcome of vascular remodeling and the fate of atherosclerotic plaques.

To summarize, our data show that expression of uPA and its receptor, uPAR, may be detrimental in promoting age- and atherosclerosis-associated morphological and pathophysiological changes in the vascular wall, both systemically and locally.

2.4 uPA/uPAR System Therapeutic Perspectives

A wide variety of functions exerted by the urokinase system in the vascular wall make it an attractive therapeutic target. Cleaved forms of uPAR, in particular suPAR, are found in biological fluids like plasma and urine. suPAR has recently been proven to serve as a marker and mediator of multiple inflammatory, cardiovascular, and kidney diseases. These findings explain the boosting interest in research and development of therapeutic approaches for targeting the uPA/uPAR system. Historically, uPAR has been considered as an attractive therapeutic target in the field of cancer treatment. Tumor tissues express high levels of uPAR, which has multiple roles associated with cancer progression and metastasis. Originally, therapeutic attempts aimed at preventing extracellular plasmin activation and proteolysis by interfering with uPA binding to uPAR. Peptide and small-molecule inhibitors were developed based on the structure of the uPAR growth factor domain to prevent uPA binding (Mazar et al. 2011). A panel of antibodies blocking uPA–uPAR binding has also been reported. However, in contrast to genetic knockdown experiments providing

strong evidence that decreased uPAR expression has robust antitumor effects, pharmacological inhibition of uPA/uPAR binding was minor (O'Halloran et al. 2013).

A number of novel proof-of-principle approaches targeting the uPA/uPAR system have been recently reported. Though uPAR is a GPI protein lacking a transmembrane domain, it may interact with a number of membrane proteins, such as growth factor receptors, integrins, and caveolin, as well as the ECM protein, vitronectin, resulting in pleiotropic activation of various intracellular signaling pathways. This has led to the hypothesis that targeting uPAR protein–protein interactions may be an effective therapeutic anti-uPAR tool. A number of peptide inhibitors have been developed for targeting uPAR–integrin interactions (Rabbani and Gladu 2002). Peptide inhibitors have attracted an enormous rise in interest as a new exciting therapeutic tool. At present, about 60 peptides are marketed worldwide, about 270 peptides are in clinical trials, and approximately 400 are in preclinical research phases. However, there has been little progress in targeting the uPAR–integrins interactions.

To conclude, despite the extensive accumulation of knowledge of uPA/uPAR biology and functions, this remarkably multifunctional system warrants further investigation as a promising diagnostic and therapeutic target, especially regarding vascular disease and aging.

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Chapter 3
Impact of Metabolic Control on Cognitive Function and Health-Related Quality of Life in Older Diabetics

Anna Marie Herghelegiu and Gabriel Ioan Prada

3.1 The Global Burden of Diabetes Mellitus at Older Ages

Life expectancy and prevalence of diabetes mellitus (DM) are rising all over the world. Consequently, an increasing number of older people will be living with and managing this disease and its complications. During the last decade, more and more reports on diabetes prevalence from nations across the world have led to an increasing awareness that this is a huge health issue with massive costs affecting all countries. In 2011, there were 52.6 million people with DM (20–79 years old) in Europe and 366.2 million worldwide. Projections for 2030 show a 22 % increase in Europe and 51 % globally (IDF 2011). In people over 60 years old, the prevalence of diabetes is nearly seven times that of the 20–39 age group. It has been estimated that over 60 % of diabetics will be over 60 years old by 2030 (Shaw et al. 2010). Diabetes and cerebrovascular disease were among the first 20 leading causes of disease burden in 2004, and are projected to move up three or more places in the ranking by 2030 (WHO 2008).

Not only will the burden of diabetes continue to rise as the world's population ages, but the prevalence of other advanced age-associated pathologies, such as dementia, will also increase. Dementia is recognized as a disabling disease with major economic and social consequences. Alzheimer's disease (AD) and other dementia contribute 4.1 % of all disability-adjusted life years (DALYs) worldwide,

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11.3 % of years lived with disability, and 0.9 % of years of life lost among people aged 60 and over (Murray and Lopez 1996; Fuster and Voute 2005). According to the World Alzheimer Report, in 2010, the prevalence of dementia among 60-year-olds and older was 6.2 % in Europe and 4.7 % worldwide (Prince and Jackson 2009). It has been estimated that during the next 20 years, the number of people over 60 years of age diagnosed with dementia will increase by 40 % in Europe and by a staggering 85 % across the globe (Prince and Jackson 2009). Because there is no known cure for this disease, early diagnosis and risk factors recognition are extremely important. Early diagnosis allows time for planning lifestyle changes and adjustments, organizing patient and family support, education and acceptance of living with this condition, as well as access to specialized care and early therapeutic intervention, which is crucial for delaying further cognitive decline. The 2011 World Alzheimer Report has estimated that approximately 28 million of the 36 million people with dementia have not been formally diagnosed yet, and therefore do not have access to treatment, care, and organized support, which a formal diagnosis can provide (Prince et al. 2011).

3.2 Mechanisms of Cognitive Decline in Type 2 Diabetes Mellitus

The most common type of dementia is Alzheimer's disease, accounting for an estimated 60 % of all dementia cases (Alzheimer's Association 2013). Recent studies have highlighted combined pathological pathways (Alzheimer's, vascular, and Lewy bodies dementia) involved in mixed dementia, a form of dementia much more common than previously thought (Schneider et al. 2007; Jellinger and Attems 2007). Most types of dementia, like Alzheimer's and Lewy body disease, are progressive and irreversible; however, some types of dementia, such as those caused by metabolic imbalance, may be reversible if diagnosed and treated early.

Even a moderate association between diabetes and cognitive decline could have great public health implications. In the last few years, more and more evidence has been suggesting that diabetes contributes to cognitive decline in older people, adding a negative impact on compliance and adherence to medication and lifestyle changes, as well as on motivation, quality of life, and well-being. Today it is widely recognized that DM acts as a risk factor for dementia (for a review of the contribution of lifestyle factors to dementia, see Qiu 2014).

There are two main categories of risk factors for dementia: non-modifiable and modifiable. The main non-modifiable risk factor for Alzheimer's disease is considered to be advancing age, because the prevalence of this condition doubles every 5 years after the age of 65 (Prince and Jackson 2009). Other non-modifiable risk factors are a family history of AD and isoform $\varepsilon 4$ of the *apolipoprotein E* gene (*ApoE ε4*). Apolipoprotein E is a protein found in the blood that binds lipids and mediates lipid transport and uptake, while the *ApoE ε4* gene has been implicated

in several pathologies such as atherosclerosis, ischemic cerebrovascular disease, multiple sclerosis, and Alzheimer's disease. Individuals with mild cognitive impairment (MCI), especially the amnesic-type, are more likely to develop AD or other forms of dementia, while in some cases MCI is in fact an early stage of dementia (Alzheimer's Association 2013). The modifiable risk factors are the ones that could and should be aggressively addressed and treated. These include education, social and cognitive engagement, traumatic brain injury, and cardiovascular disease risk factors (for a review of social and behavioral influences on later cognitive function, see Leist and Mackenbach 2014). Cardiovascular disease risk factors include smoking, DM, obesity, hypertension, and high cholesterol in midlife or metabolic syndrome, and are associated with a high risk of cardiovascular diseases as well as a higher risk of developing AD and other types of dementia (Kaffashian et al. 2013; for a review of obesity and cognitive aging, see Dahl Aslan 2014).

Diabetes mellitus could lead to cognitive impairment through a broad range of processes, including alterations in blood sugar levels (several disturbances in blood sugar and cardiovascular regulation, such as chronic hyperglycemia and repeated hypoglycemia), damage of small and large blood vessel walls (microvascular and macrovascular disease), and resulting cardiovascular events. Additionally, hyperinsulinemia, insulin resistance, and hypertension have each been independently related to cognitive impairment.

The pathological relationship between diabetes and cognitive decline is complex and not yet fully understood. Systematic reviews have confirmed that diabetes is strongly involved in the pathological pathways of Alzheimer's disease as well as vascular dementia, emphasizing the high prevalence of mixed dementia among older adults (Biessels et al. 2006; Mark et al. 2008). The mixed pathogenesis of cognitive decline in older diabetics has been scarcely studied, but is gaining awareness among researchers.

The augmented risk of cognitive decline might be because of synergistic actions of diabetic metabolic disorders and cerebral structural and functional age-related changes (Ryan and Geckle 2000; Biessels et al. 2002). Several studies using neuroimaging techniques have reported more cortical and subcortical atrophy and white matter hyperintensities in diabetic patients compared with age-matched control groups (denHeijer et al. 2003; Schmidt et al. 2004; Manschot et al. 2007). White matter hyperintensities are associated with high risk of stroke and dementia (Debette and Markus 2010).

While the causal relationship between ischemic vascular events and cognitive decline is clear, less is known about cerebral microvascular disease and how it might contribute to the onset and progression of dementia (van Harten et al. 2006; Tiehuis et al. 2008). Several large studies have identified an independent association between retinal vascular changes (diabetic retinopathy) as a marker of cerebral microvascular disease, and executive function, psychomotor speed decline, slow gait and depressive mood (Lesage et al. 2009; Hyun Kim et al. 2011). The hypothesized association between diabetic retinopathy (DR) and cognitive decline has also been confirmed by the Edinburgh Type 2 Diabetes study (Ding et al. 2010).

Based on epidemiological, clinical, neuroimaging techniques and interventional evidence, it has been suggested that sporadic (nongenetic) AD should be considered a vascular disorder (de la Tore 2002).

The predominant form of DM in older adults is type 2, which is characterized by peripheral insulin resistance and relative insulin deficiency. More and more evidence suggests that insulin may be directly involved in pathological pathways that lead to cognitive decline, based on the *cerebral insulin resistance* and *insulin-induced amyloid pathology* hypotheses (Biessels and Kappelle 2005). A large body of evidence supports the mechanism of cerebral insulin resistance as a player in neurodegenerative changes associated with dementia (de la Monte and Wands 2008; Williamson et al. 2012). The insulin resistance of hepatic cells generates accumulation of ceramides. Ceramides are lipid molecules found within the cell membranes of cells. These molecules have structural roles, but they also participate in a variety of cellular activities such as differentiation, proliferation, and programmed cell death. After passing the hematoencephalic barrier, the ceramides mediate cerebral insulin resistance by activating proinflammatory cytokines and inhibiting phosphatidyl-inositol-3 kinase (PI3K), thus disrupting transmission of signals through the insulin or insulin-like growth factor 1 (IGF-1) receptors, insulin receptor substrate and protein kinase B (Arboleda et al. 2007; Lyn-Cook et al. 2008). It has been demonstrated that IGF-1 has neuroprotective properties, stimulates neurogenesis and synaptogenesis, regulates brain glucose metabolism, inhibits glial inflammation by antagonizing tumor necrosis factor α (TNFα), and promotes elimination of amyloid-beta (Aβ) from cerebral tissue. Exposure to ceramides results in altered glucose utilization with low ATP levels, Aβ accumulation and hyperphosphorylation of *tau* protein (Gasparini and Xu 2003; Tong and de la Monte 2009).

Hyperglycemia can impair cognitive function by causing disruption of cerebral regional blood flow, neuronal osmotic changes and alterations in glucose transport through the hematoencephalic barrier (Brownlee 2005; Kodl and Seaquist 2008). Hyperglycemia-induced oxidative stress lesions generated by reactive oxygen species (ROS) is another pathological mechanism involved in cognitive decline (Cardoso et al. 2013; Zhao et al. 2013). It has been shown that prolonged hyperglycemia disrupts gap junction communication among astrocytes, and alters neurotransmitters' function (Gandhi et al. 2009; Roriz-Filho et al. 2009). In diabetic models an *N*-methyl-D-aspartate (NMDA) receptors disorder has been observed, resulting in deficits in long-term potentiation, especially in the hippocampus, as well as impaired alpha-amino-3-hydroxy-5-methylisoxazole-propionate (AMPA) receptors regulation during expression of long-lasting depression in synaptic function (Trudeau et al. 2004). Decreased acetylcholine and serotonin turnover, decreased dopamine activity, and increased norepinephrine levels induced by hyperglycemia have been reported in studies on streptozotocin-injected rats (Kodl and Seaquist 2008). There is little evidence on the effects of short-term or long-term hyperglycemia on cognitive function in older diabetics, and even less on the effects of hypoglycemia. There is one report on an association between severe hypoglycemic episodes and risk of dementia in older diabetics, but further confirmation is needed (Whitmer et al. 2009).

3.3 A Longitudinal Study on the Relationship Between Diabetes Mellitus, Cognitive Function, and Health-Related Quality of Life in Old Age

Older adults with diabetes experience substantial comorbidity, physical disability, and psychosocial morbidity including impaired cognitive function, lack of social independence, and increased medical service use. In this regard, it is necessary to establish new methods for controlling the risk of cognitive impairment and poorer quality of life in older diabetic patients and to improve the medical, psychological, and social care of these patients.

Very few observational prospective studies have identified a predictive value of fasting serum glucose (FSG) or glycated hemoglobin (HbA1c) levels for cognitive function in older diabetics, and interventional trials have reported conflicting results. There is not enough data on the potential impact of diabetic complications on cognitive function. The present study was designed to elucidate the associations between metabolic control and cognitive function.

Although the negative impact of diabetes on health-related quality of life (HRQoL) and well-being, especially in older patients, might be obvious, little research has been done regarding quality of life in relation to glycemic control. Some authors have reported no significant association between quality of life and HbA1c or FSG (Kleefstra et al. 2005), while others have identified a decline in physical functioning with poor metabolic control (Schlotz et al. 2007). The majorities of the available published studies that have investigated the association between metabolic profile and cognitive function or HRQoL in older diabetics have employed heterogeneous study groups, small samples, or did not include control groups, thus justifying more intense clinical research.

This study aimed at evaluating the impact of metabolic profile on cognitive function in older diabetics. Based on the hypothesis that older diabetics could have a poorer quality of life, we examined how metabolic control as well as diabetes complications and associated diseases relate to HRQoL. A secondary objective was to identify potential risk factors for cognitive decline and altered quality of life. This is an observational, prospective cohort type of study extended over a period of three years. The research was carried out at the National Institute of Gerontology and Geriatrics "Ana Aslan", Bucharest, during 2008–2011. The institutional review board was consulted for ethical approval prior to initiating the study.

The study group included 360 participants, who were inpatients referred by their GPs or other specialists for various subacute or chronic conditions. The control group included 300 participants of similar age, socio-demographic, and cultural profiles, without diabetes or altered glucose tolerance, who were also inpatients referred for a variety of pathologies. All participants were selected based on inclusion and exclusion criteria and after signing an informed consent. The inclusion criteria were: patients 65 years of age or older, with a prior diagnosis of DM or newly diagnosed with this disease at baseline; patients living independently in their

communities. The exclusion criteria were: prior or de novo diagnosis of dementia, diagnosis of cancer during the last 5 years, terminal conditions, advanced heart failure, or patients living in nursing homes.

According to the study objectives, metabolic profile, diabetes complications and associated diseases, therapeutic management, cognitive function, and HRQoL were monitored longitudinally with extensive assessments of medical history, health behaviors, neurological and physical assessments, and of biomarkers obtained from blood and urine tests. Patients were initially admitted for baseline assessment and afterwards every 6 months for reevaluation, with a total of four assessments. The dropout rate between assessments in the study group varied between 20.56 % at 6 months and 31.12 % at 18 months. Participants missing follow-ups were contacted by phone (all patient contact details were registered at baseline). Analyzing the responses, the main reasons for attrition were personal situations not related to health status, living a long distance away from the hospital and various mild health problems not associated with diabetes or cognitive status. Participants missing more than one evaluation were excluded from the study (17.43 %). After determining randomness, missing data were managed using the expectation maximization technique. In detail, the assessments included documented medical history, age, sex, and socio-demographic and cultural profile, current medication, smoking and alcohol consumption, physical examination (including neurological exam), daily clinostatic and orthostatic blood pressure and heart rate, body mass index (BMI), waist/hip ratio, electrocardiogram (ECG), chest X-ray, peripheral circulation (either Duplex Ultrasonography or ankle-brachial index test), retinal examination, cognitive function, HRQoL, and biological profile. Biological evaluation consisted of: metabolic profile (FSG, HbA1c, and lipid profile), liver transaminases, serum urea and creatinine levels, creatinine clearance, serum uric acid levels, protein electrophoresis, erythrocyte sedimentation rate, complete blood count, and urinalysis (test strip and microscopy examination).

Quantitative cognitive assessments were performed using the Folstein Mini Mental State Examination (MMSE) and the Clock Drawing Test (CDT). These standardized instruments have proven to be feasible for monitoring changes in cognitive function in prospective studies on patients with dementia or delirium, for screening and comparative studies, as well as for diagnosis, response to treatment, severity appraisal, and as a base for further in-depth evaluations (Woodford and George 2007; Pinto and Peters 2009). MMSE and CDT correlate well with each other as well as with other cognitive screening tests (Juby 1999). Better performance (higher sensitivity and specificity) has been proven when a combination of instruments is used for assessment of cognitive decline (Stahelin et al. 1997; Samton et al. 2005). The MMSE instrument evaluates five domains of cognitive function: orientation (time and space), recall (immediate and short-term recall), attention and calculation, ability to follow verbal and written commands, and language and visual construction (Folstein et al. 1975). The maximum score is 30 points; a score under 27 is relevant for MCI. The CDT is a brief test that addresses executive function and visuospatial, constructional praxis, accounting for comprehension, planning, abstraction, visual memory and image reconstruction, motor programming and execution, and concentration (Pinto and Peters 2009). Because a decline in executive

function has been shown to precede memory loss, the CDT was used to identify early cognitive decline in patients with normal MMSE scores (Binetti et al. 1996; Royall et al. 1999). There are several scoring and interpretation models for the CDT. We used the ten points scoring system described by Sunderland et al. (1989), because it has been proven to be more sensitive to cognitive changes in patients with normal MMSE scores (Sunderland et al. 1989; Juby et al. 2002). A score of at least six points is considered normal.

Quality of life was monitored by the SF-36v2™ Health Survey, a standardized questionnaire for functional health and well-being evaluation. It was developed by specialists from the international corporation "Research and Development" (RAND) as a generic instrument for functional health, psychological and emotional well-being assessment from the respondents' own perspective (Ware and Sherbourne 1992). The instrument has proven its excellent psychometric properties, high acceptability and completion rate, and has been widely used in a large number of trials and studies on adults of old age (Haywood et al. 2005; Alesii et al. 2007). It has also been used successfully in studies with older diabetic patients (Luscombe 2000; Speight et al. 2009). This instrument has a wide array of applications from measuring the impact of various conditions on HRQoL and assessing benefits of treatment, to burden of disease and administrative research across populations or specific groups. The questionnaire includes 36 questions addressing eight health domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning (SF), role-emotional (RE), and mental health, either at present state or during the last 4 weeks (Ware and Sherbourne 1992). Social functioning was evaluated by enquiring about the amount of time in the last 4 weeks the subject's physical health or emotional problems have hindered his/her social activities such as visiting friends or relatives. Role-emotional limitations were assessed by asking the respondents how often in the last 4 weeks emotional problems such as feeling depressed or anxious have led to accomplishing less work or daily activities than desired. The mental health domain included questions about how the subject has been feeling in the last 4 weeks, such as nervous, calm and peaceful, tired and worn-out or happy. The respondents filled in the standardized Romanian adapted form of the questionnaire. When required by specific situations (i.e., illiteracy or poor vision), the questionnaire was administered by interview.

Microvascular complications (e.g., retinopathy, neuropathy, and nephropathy), macrovascular disorders (e.g., history of acute myocardial infarction or ischemic heart disease, ischemic ECG patterns, stroke and peripheral arterial disease), cardiovascular risk factors [e.g., hypertension or hypertension medication, smoking, dyslipidemia or lipid lowering medication, BMI, waist/hip ratio, and alcohol consumption], diabetes management (three groups of patients were considered either on diet, oral medication, or insulin), and the number of diabetes complications were included as covariates. Participants smoking less than ten cigarettes per day or smoking during the last 5 years were considered "smokers", while participants smoking more than ten cigarettes per day were considered "heavy smokers". We defined "occasional alcohol consumption" as drinking less than once a week and a maximum of 250 mL of wine, 500 mL of beer, or 50 mL of spirits, and

"chronic alcohol consumption" as drinking more than one drink per week and more than 250 mL of wine, 500 mL of beer, or 50 mL of spirits. Management of diabetic patients included low carbohydrates diet only, oral medication (such as agents that increase the glucose utilization by target organs, medication that stimulate insulin release by the pancreas or agents that decrease the absorption of carbohydrates from the digestive tract), or insulin, based on medical recommendation in each individual case as required by the patient's health status at the time of assessment. The average hospitalization time at each follow-up evaluation was ten days during which medication was administered by nurses and patients received meals according to their recommended diet.

Raw and mean total and domain scores of the MMSE, CDT, and SF-36v2™ were used as dependent variables. In line with the SF-36v2™ questionnaire standard protocol, mean domain scores substituted for related missing values when the respondent answered at least half of the questions. The gross scores were converted to a 0–100 points scale (0—worst health status, 100—best health status) after being corrected and recalibrated.

Mean score values of cognitive function and HRQoL tests in the study and control groups were compared at baseline using the independent *t*-test. A mixed design analysis of variance (split-plot ANOVA) was employed for assessment of metabolic control effects at repeated measures on cognitive function and HRQoL in diabetic and control groups. The Bonferroni correction was used to control the familywise error rate. Subsequent One Way ANOVA and repeated measures ANOVA tests were conducted to identify significant changes in cognitive function and HRQoL at 6, 12, and 18 months considering therapeutic management groups (diet, oral medication, and insulin). Multiple linear regression models were designed to identify the predictive value of potential risk factors for cognitive function. The same analysis was used to evaluate the potential relationship between diabetes complications and HRQoL. A p value <0.05 was considered statistically significant. Statistical analysis was performed using the DATAPLOT program. A detailed overview of data analysis has been documented internally; herein, only a summary of the results of the statistical tests is provided.

3.3.1 Profile Description and Baseline Features

The study and control groups were comparable in the main socio-demographic characteristics. The mean age was 69 and 68 years in the study group and the control group, respectively. Three levels of education were defined: primary school (4–8 years of education; 31 % of participants in the study group and 32 % in the control group), high school (10–12 years of education; 37 % in the study group; and 41 % in the control group), and college or university (>14 years of education; 32 % in the study group; and 27 % in the control group) (Herghelegiu and Prada 2009).

Analyzing the presence of risk factors for cognitive decline, a higher percentage of non-smokers, abstinence from alcohol consumption, and a lower percentage of

dyslipidemia were recorded in the study group compared with the control, but also higher percentages of overweight, obesity, and hypertension.

A DM diagnosis was confirmed within the last year or de novo in 32.77 % of patients. The duration of DM was one to 5 years in 21.66 % of patients, 5–10 years in 22.77 %, and longer than 10 years in 22.77 % of patients. As recorded at baseline, diabetes was managed by diet alone in 38.33 % of patients, while 46.94 % of patients were receiving oral anti-diabetic medication (OAD) and 14.72 % of patients were insulin dependent.

The distribution of diabetic complications was highest in all forms of neuropathy (54.15 %) and lowest in nephropathy (1.11 %). No diabetic complications were identified in 28.05 % of patients, while 20.27 % had retinopathy and 23.33 % presented peripheral arterial disease.

MCI was considered in patients with an MMSE score of 21–26. The initial evaluation of cognitive function with MMSE identified MCI in 15.8 % of diabetic patients. There were no significant differences in the overall cognitive scores (MMSE and CDT) between the diabetic and control groups. However, recall, attention, and calculation performances (MMSE domain scores) were statistically poorer in diabetic patients compared with control ($p=0.01$; $p=0.03$). There was no significant difference in the overall SF-36v2™ scores except for the role-emotional and mental health domains, which were lower in the study group ($p=0.04$, $p=0.02$, respectively; Herghelegiu and Prada 2009).

3.3.2 Changes in Cognitive Function

The overall cognitive scores (MMSE and CDT) had a descending trend during the 18 months of monitoring in all participants, and a group effect was identified considering diet, oral medication, or insulin administration in diabetic participants (Fig. 3.1). Significant changes in cognitive function (MMSE) were not confirmed at any of the follow-up evaluations ($p>0.05$).

However, the attention and calculation scores significantly declined during follow-up in diabetic patients compared with control participants. The recall function scores were significantly lower in the study group compared with control, but the deterioration was not significant during the study period. A group-by-time interaction effect on cognitive function was determined: at 18 months, the CDT scores were significantly lower in the study group compared with the initial evaluation and with the control group (Herghelegiu and Prada 2011). Cognitive changes were analyzed in two interest groups: participants with normal MMSE and patients with MCI. The linear regression model of analysis showed a significant decline in cognitive function in MCI participants.

First, differences in trajectories of cognitive function and HRQoL were assessed between the study and control groups. Significant declines in both MMSE and CDT scores were highlighted at various stages of evaluation in all therapeutic groups. Comparison of the CDT scores in the diet group showed a significant deterioration in

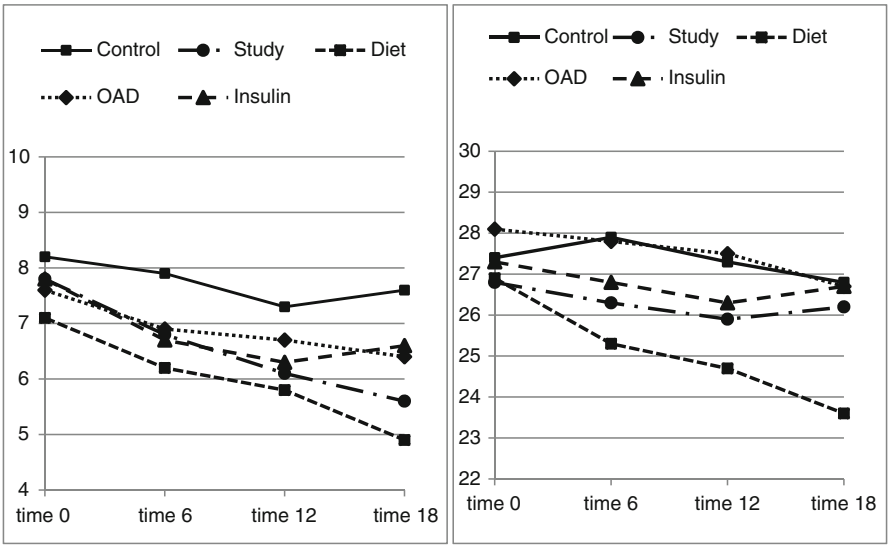

Fig. 3.1 Trends in mean CDT (*right*) and MMSE (*left*) scores in different therapeutic groups over 18 months of evaluation ("study" group included all participants with all three different therapeutic recommendations)

cognitive function at all follow-up stages compared with the control group ($p<0.05$). Patients in the diet group had significant lower CDT scores at 12 months compared with patients receiving oral medication, and at 18 months compared with both OAD and insulin groups ($p<0.05$). Comparison of the mean MMSE scores identified a significant cognitive decline at all follow-up stages in patients on diet compared with both control and OAD groups, and at 18 months compared with the insulin group ($p<0.05$). During follow-up, the cognitive function was most impaired in the diet group, where mean CDT scores were significantly lower at 18 months and mean MMSE scores were significantly lower at all stages (Herghelegiu and Prada 2011).

Next, the predictive value of the metabolic indicators, FSG and HbA1c, on cognitive scores was assessed. The first set of analyses showed that there were no significant variations in FSG and HbA1c levels over time and between groups. A multivariate linear regression model was used to verify which determinants influence cognitive scores. A significant relationship was identified between CDT scores and HbA1c, between both cognitive scores and DM duration in years, and between CDT scores and BMI.

Considering the indications obtained thus far, several models were designed to analyze the adjusted impact of metabolic control on cognitive function. This was done by building a base model with age, sex, education, and one of the metabolic indicators as covariates, and separately including one of the other factors as an additional covariate. The following covariates were used: duration of DM in years, hypertension or current hypertension medication, dyslipidemia or current lipid lowering medication, smoking habits, alcohol consumption, BMI and waist/hip ratio, microvascular diabetic complications, and macrovascular diabetic complications.

The relationship between HbA1c levels and CDT scores remained significant after adjusting for other variables with the exception of chronic alcohol consumption and duration of DM. The association between cognitive scores and duration of DM persisted after controlling for all other determinants. The association between CDT scores and BMI maintained its significance when adjusting for age, sex, education, smoking habits, and microvascular complications. There was no significant interaction between FSG and cognitive scores ($p > 0.05$) (Herghelegiu and Prada 2011).

3.3.3 Changes in Health-Related Quality of Life

The same statistical analysis as for cognitive changes was performed for HRQoL evaluation. The overall MMSE and CDT scores were considered covariates. There was a descending trend in the overall SF-36v2™ scores in all three therapeutic study groups (diet, OAD, and insulin); however, it was not significant. No group effect was identified, although insulin-dependent patients did report better overall HRQoL scores as opposed to patients on a diet, who recorded the lowest scores out of all therapeutic managements. There was a significant positive relationship between HRQoL and cognitive function when MMSE scores were transformed into binary variables (normal cognitive function and MCI). However, after adjustment for duration of DM, this association lost significance ($p > 0.05$). The repeated measures analysis of variance used in each of the SF-36v2™ domains recognized a group-by-time interaction for RE and SF. The other SF-36v2™ domains did not significantly change during monitoring and were not significantly different compared with the control group ($p > 0.05$).

3.4 Discussion and Conclusions

The results of this prospective observational study bring new evidence supporting the hypothesis that DM is an independent risk factor for cognitive decline in older people without dementia. The cerebral biochemical and structural changes gradually take place well before any clinical signs of cognitive deterioration appear. These results indicate that DM could accelerate cognitive decline acting as a predisposing factor, especially when MCI has already been diagnosed. In our sample, the number of participants with MCI was too small to further analyze other determinants. The results confirmed that there is a relationship between metabolic parameters (HbA1c) and cognitive test scores. Similar outcomes have been reported in a series of studies that have shown a significant association between the presence of DM and cognitive performance (evaluated with the MMSE) in older diabetics without dementia (Arvanitakis et al. 2006; Alencar et al. 2010). In this study however, the same association between DM and cognitive function was significant, but only in the CDT and not the MMSE scores, perhaps emphasizing the earlier decline in executive function. A recent trial found a significant correlation between metabolic parameters in diabetes (HbA1c and not FSG) and cognitive test scores (MMSE)

(Cukierman-Yaffe et al. 2009a). In another large study, a strong association between FSG levels and MMSE scores was identified (Cukierman-Yaffe et al. 2009b). This trial also adjusted the analysis for a number of determinants such as education and cardiovascular risk factors, and the association remained significant in all models. In our study, the results suggest that with longer duration of DM, there is a weaker association between metabolic parameters and cognitive scores. This observation is even more interesting, because the data collection spanned over a short period of only 18 months. Referring our results to the reports of the intervention arm of the trial cited earlier (Cukierman-Yaffe et al. 2009a) and to other intervention studies, which have failed to confirm an improvement in cognitive scores with more aggressive glucose lowering therapies, it is important to emphasize the hypothesis that once the cerebral changes start happening in a diabetic patient, lowering the metabolic parameters will not reverse the process. Therefore, a close detailed monitoring of cognitive function and rigorous metabolic control may be imperative, especially in the very early stages of DM or altered glucose tolerance. Several years after diagnosis of DM, metabolic control may not lead to gain in cognitive function anymore, so to maintain cognitive function, early treatment is essential.

No significant relationship between FSG and cognitive tests' scores was identified in our study. A possible explanation might be the age profile of the study sample, older patients being less compliant to diet instructions before blood test and more sensitive to stress. However, neither HbA1c levels nor FSG levels have significantly varied throughout the study duration. Even though a group-by-time interaction was observed for cognitive scores in different therapeutic management groups, the levels of metabolic parameters have been consistent both in time and between groups. This particular aspect might be because of the observational nature of the study, patients being treated according to guidelines and based on their metabolic parameters, but other determinants might also influence cognitive function in patients on diet alone. The study sample was too small to conduct further analyses on specific interest subgroups.

A negative impact of DM on HRQoL was present but not significant during monitoring. A significant deterioration was identified only in role-emotional and social functioning. In patients with MCI, there was a positive association between cognitive function and HRQoL decline. After adjustment for duration of DM, the statistical value of this association was lost. Here, studies with a longer time span are needed for further information. Also, a drawback of this study is the absence of monitoring of depression symptoms. There was no group-by-time interaction for HRQoL considering different therapeutic management groups. Other determinants did not significantly affect HRQoL in older diabetics. An earlier large interventional trial did not confirm any benefits of intensive glucose lowering management in HRQoL, but reported a significant negative impact of macrovascular disorders on general health, vitality and daily activities, and of microvascular complications on emotional status (U.K. Prospective Diabetes Study Group 1999). A more recent study that used the SF-36v2™ instrument in diabetic patients aged 30–70 years described lower scores of physical functioning, social functioning, and mental health domains in patients with poor metabolic control (Imran Kamarul et al. 2010).

This is the first study evaluating the impact of DM on cognitive function and HRQoL in older patients without dementia in Eastern Europe (considering available papers cited by publication databases) and one of the few longitudinal observational studies on participants of older age. The main strengths of the study are the homogeneity of sample groups and the availability of data from a prospective monitoring of a large number of related determinants and potential risk factors. The results of our study contribute to the accumulation of observational evidence calling for more large interventional trials. Studies on frail diabetic older adults over the age of 85 years are also needed, as this segment of population is growing rapidly along with increased life expectancy and improvements in medical technologies and medical care accessibility. For a more complete picture of the pathological pathways and clinical practice implications of the effects of diabetes mellitus on cognitive function, research on older adults with a diagnosis of dementia or MCI prior to that of DM could also be of interest.

3.5 Conclusions

For proper management of an older diabetic patient, routine medical care should include combined tests directed at cognitive function evaluation. A good metabolic control (confirmed by regular HbA1c tests) contributes to the preservation of cognitive status; however, this is only in early DM and it becomes less important with increasing duration of DM. Addressing other risk factors, especially alcohol consumption and BMI, is also necessary. Once the first signs of cognitive impairment appear, the presence of DM will most likely accelerate the decline. It is to be expected that DM has a negative impact on patients' quality of life, particularly limiting social functioning and affecting emotional status. The type of therapeutic approach for metabolic control does not appear to influence HRQoL of older diabetics without dementia. Effective and early diabetes management in older patients is not only highly desirable to prevent diabetes complications, morbidity, and premature mortality, but also to maintain healthy levels of cognitive functioning and HRQoL for as long as possible.

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Chapter 4
Understanding the Mechanisms of Immune System Aging: Immune System Cell Development and Antibody Repertoires

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4.1 Introduction

With the increasing life expectancy and rapid growth of the older adult population, the frequency of age-related diseases, such as infectious diseases, autoimmune syndromes, and various forms of cancer, is increasing in the population. Therefore, society must face these issues and their related problems, including the increasing costs of health care. The first step in addressing these issues is to determine how the immune system changes during aging.

It is clear from a wide variety of model organisms that aging can be significantly postponed by several manipulations that affect nutrient sensing (such as dietary restriction; Kenyon 2010) and cellular metabolism (Blagosklonny 2012; Harrison et al. 2009; Ladiges et al. 2009). This observation has two key implications. Firstly, it is likely that the fundamental cause of cellular aging lies, at least in part, in metabolic changes. Secondly, successful interventions that can extend the global healthspan (the number of years lived in a healthy, vital state) seem within the reach of biomedical scientists studying the biology of aging.

Individual biomedical disciplines improve the quality of life for older adults by alleviating or mitigating the most frequent adverse effects of aging and age-related diseases. In this context, infectious diseases remain a serious threat to older adults,

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taking a massive toll in morbidity and mortality among that population (Bender 2003; Gardner 1980). The age-related decline in the function of the immune system itself, also called "immunosenescence," is undoubtedly the principal cause of the poor vaccine responses in this population, and is probably a major factor in the increased susceptibility to infections with increasing age. Aging research and immunology are both incredibly complex disciplines and we must study them simultaneously to understand how and why the immune system ages, and what can be done to improve and prolong its function. Evidence of age-related changes in the immune system has come from studies of both mice and humans. These studies aim to understand how and why the immune system ages, and how the aging of specific elements of the immune system contributes to reduced immune protection. Some obvious indications of a decline in immunological function are an increased sensitivity to emerging pathogens, reduced responsiveness to vaccination, an increased occurrence of cancer, and an increased incidence of chronic inflammatory processes and some autoimmune syndromes (Geiger and Rudolph 2009; Johnson et al. 2002; Kline et al. 1999; Thompson et al. 2003; for a review on aging-related changes in the immune system and perspectives for intervention, see Herndler-Brandstetter 2014). It is widely agreed that many of the aging-related changes in adaptive immunity are attributable to changes in the dynamics of B cells. However, the mechanisms of these age-related changes in B-cell functions have not yet been clarified. In this chapter, we review the current findings on the aging-related changes in B-cell population dynamics, repertoires, and functions. The remainder of the chapter is structured as follows. Firstly, an overview of how immune responses lead to the production of antibodies by B cells is given, followed by a description of how B cells develop. Aging-related changes of the immune system are then described, with an emphasis on the changes that occur in B-cell development and function.

4.2 The Antibody Response in Healthy Individuals

When a foreign object such as bacteria or viruses, which are infectious agents (pathogens), enters the body, the immune system produces antibodies against it. The antibody response involves highly specialized immune cells (termed white blood cells) that eliminate the pathogens or prevent them from causing disease in the host. B lymphocytes are white blood cells that recognize the pathogens and produces antibodies against them. Each antibody has a unique binding site which binds to specific sites in the pathogens. The antibodies destroy the pathogen which is then being engulfed and digested by other immune cells called macrophages.

4.2.1 How the Immune System Deals with Pathogens

The adaptive immune response recognizes and remembers specific antigens (any substance that causes the immune system to produce antibodies against it), and mounts a stronger response each time the same antigen is encountered. T and

B lymphocytes carry receptors that specifically recognize antigens. Adaptive immunity has four major characteristics: (1) antigen specificity; (2) diversity; (3) immunological memory; and (4) the ability to differentiate self from nonself cells. B lymphocytes are white blood cells involved in the antibody response. They recognize pathogens (infectious agents) via their B-cell receptors (BCR), which recognize, bind, and internalize specific antigens (Kim et al. 1993). The BCR is a receptor protein located on the outer surface of B lymphocytes. The receptor has a unique and randomly determined antigen-binding site. It is composed of two types of protein chains, the immunoglobulin heavy chains (IgH) and immunoglobulin light chains (IgL) (Matsuuchi and Gold 2001).

Binding of the BCR to a pathogen provides the cell with an activation signal (Kim et al. 1993). Most activated B cells become short-lived plasma cells or plasmablasts, which secrete antibodies and die after several days, whereas others develop into either long-lived plasma cells residing in the bone marrow (Elgueta et al. 2010; Radbruch et al. 2006; Shapiro-Shelef and Calame 2005) or into memory B cells, which remain in the body to be activated by encounters with the same antigen (LeBien and Tedder 2008). Memory B cells are more specific to the antigen they have previously encountered and are activated much faster than naïve B cells, which must mature and differentiate (Monroe et al. 2003; Tangye et al. 2003).

Lymph nodes are found throughout the body and, together with the spleen, are charged with a *crucial function* in the mammalian immune system. The lymph nodes and spleen contain germinal centers (GC; Willard-Mack 2006), which develop following T-cell-dependent antigen activation of B cells and are composed primarily of B cells. GCs develop within 9–30 days of exposure to an antigen, depending on the strength of the immune response (Allen et al. 2007), and are the main sites of high-affinity plasma cell and memory B-cell generation. GCs also contain small numbers of $CD4^+$ T cells (T follicular helper or Tfh cells), which are required for GC development, persistence, and function. GC B cells undergo rapid clonal expansion, somatic hypermutation (SHM) of the variable part of the BCR genes, and selection for the most compatible receptor (LeBien and Tedder 2008; Schroeder and Cavacini 2010). The B cells expressing the hypermutated Ig gene undergo positive selection for cells with improved affinity for the antigen and negative selection for those cells whose receptors are damaged or lost during SHM (Roulland et al. 2008). The B cells with improved affinity later become long-lived memory cells or preferentially plasma cells (Liu and Arpin 1997).

4.3 B-Cell Development

Newly generated B cells pass through various developmental stages, during which their gene expression profiles and locations change to allow them to mount an immune response. Progenitor B cells are produced in the bone marrow from lymphocyte progenitors after their commitment to the B-cell lineage with the expression of several transcription factors (Nutt et al. 1998). The IgH genes of the cells are rearranged in the pro-B-cell stage. If this occurs, the cell differentiates to a

pre-B cell (Matsuuchi and Gold 2001). Light chain gene rearrangements then occur and a complete BCR is produced and expressed on the immature B-cell surface (Schroeder and Cavacini 2010). When gene rearrangement is unsuccessful in a B cell or the cell is negatively selected because it binds self molecules, it undergoes cell death or receptor editing (Luning Prak et al. 2011). To prevent potential autoimmune responses, autoreactive B cells are eliminated by negative selection in the bone marrow and spleen (Monroe et al. 2003) during these transitional stages (Palanichamy et al. 2009). Newly formed B cells stay in the bone marrow or migrate to the spleen and then mature via several transitional stages (Allman and Pillai 2008; Chung et al. 2003; Sims et al. 2005). Transitional B cells mature into naïve B cells simultaneously in the spleen and bone marrow (Cariappa et al. 2007).

4.3.1 The B-Cell Response to Antigen Exposure

B cells play a unique role in the vertebrate immune system, producing antibodies that can neutralize invading pathogens. Importantly, these antibody responses are highly antigen-specific and generate immunological memory; upon a second encounter, the same pathogen is eliminated much more efficiently. These adaptive capacities are the result of two independent developmental stages. Firstly, each B cell creates a unique antibody during antigen-independent precursor differentiation in the bone marrow, which is expressed on the BCR. Together, all the newly produced B cells have a huge repertoire of antigen receptors with the potential to specifically recognize a vast array of different pathogens. The second phase of development begins when a B cell actually recognizes an antigen in the peripheral lymphoid organs. These activated B cells undergo enormous proliferation, thereby generating huge numbers of daughter cells that recognize the same pathogen. B cells that originate from this expansion and have undergone selection for high-affinity BCRs generate both *strong* responses and long-term memory in the form of memory B cells and Ig-producing plasma cells.

4.4 The Immune System Is Affected by Aging

The aging of the immune system affects the development of lymphocytes, starting with their early progenitors. Lymphocyte development is critically dependent on specialized cellular microenvironments in the bone marrow and the thymus, which undergo dramatic age-related changes. Moreover, lymphocyte development itself rapidly declines with aging. T- and B-lymphocyte precursors in elderly humans and animals do not develop as robustly as they did during their youth. In the case of T cells, this decline occurs during adolescence with thymic involution.

The aging immune system may be a victim of its own success, because memory T- and B-cell populations expand with increasing age, but at the expense of decreasing naïve populations, which are critical for the development of adaptive immunity to newly encountered pathogens.

In the following section, the age-associated changes in the immune system will be described. Firstly, we present evidence of age-associated defects in the generation of early B lymphocytes. Secondly, the age-associated changes in B-cell maturation and homeostasis are discussed; and thirdly, evidence of compromised B-cell maintenance and function is presented. Lastly, we provide evidence of impaired responses to vaccinations in older humans.

4.4.1 Age-Associated Defects in Early B Lymphopoiesis

The age-associated decline in immune function can be traced, in part, to the increased dominance of antigen-experienced B cells, presumably at the expense of newly generated naïve B cells (Guerrettaz et al. 2008; Johnson et al. 2002). Features of immunological aging can be induced in young mice by reducing the available pool of lymphocyte precursor cells (Guerrettaz et al. 2008). Limiting this pool leads to a reduced output of B-cell progenitors and to changes in the peripheral B-cell repertoire resembling the repertoire seen in aged mice (Guerrettaz et al. 2008). Most studies of the effects of aging on lymphocyte precursors and their functions have been performed in mouse models, but more recent work has demonstrated similarities in the effects of aging in mice and humans (Kuranda et al. 2011; Pang et al. 2011). The ability of lymphocyte precursors taken from aged humans to generate lymphoid progenitors is impaired (Kuranda et al. 2011; Pang et al. 2011).

In aged animals, lymphocyte precursors exhibit less efficient homing to the bone marrow and a delayed proliferative response compared with those of young animals. Aged precursor cells also demonstrate a reduced engraftment rate upon transplantation (Dykstra et al. 2011). These results are consistent with those of earlier studies, which reported that the age of a bone-marrow donor is the only factor to significantly predict the success of bone-marrow transplantation (Kollman et al. 2001).

Our recent studies, in collaboration with Melamed et al. (Keren et al. 2011a, b), suggest the existence of a feedback pathway capable of influencing the output of B-cell progenitors from the aged bone marrow. The systematic depletion of mature B cells in old mice led to an increase in B-lymphocyte development in the bone marrow of these aged animals (Keren et al. 2011a). We also found that in mutant (CD19-knockout) mice in which the survival of mature B cells was compromised, B-lymphocyte development did not change substantially with age (Keren et al. 2011a). Our mathematical model of B-cell development in the bone marrow and spleen suggests that the limited space and resources in the bone marrow affect B-cell development in aging mice (Shahaf et al. 2006). Our model also explains some of the decline in B-cell production under the assumption that static cells in the bone marrow and spleen, which represent the antigen-experienced B-cell compartment that may return from the periphery to the bone marrow, limited B-cell production in the bone marrow of aged mice (Shahaf et al. 2006). This model is supported by studies that have shown that there are more antigen-experienced B cells in old animals than in young animals (Johnson and Cambier 2004; Johnson et al. 2002). Those cells can be represented by the static cells in our basic mathematical model,

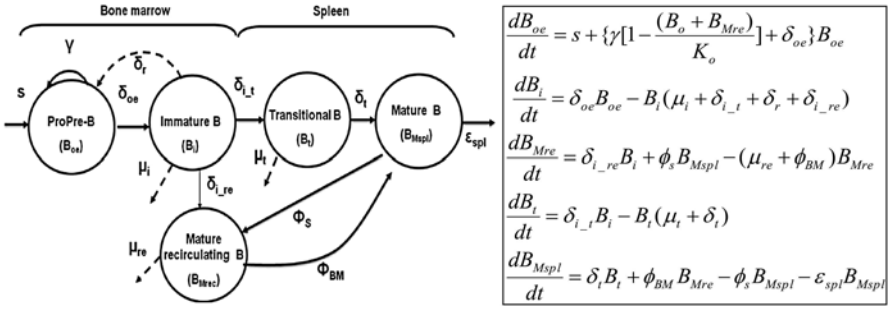

Fig. 4.1 Model of B-cell populations in the bone marrow and spleen. A model of maturing B-cell populations in the bone marrow and spleen is shown. All population processes—differentiation, proliferation, and death—are described by *arrows*. The rate of each process is given near the corresponding *arrow*. *S* source of B-lineage precursors, δ differentiation rate, μ mortality rate, γ proliferation rate, Φ inflow rate, *e* exit rate

and are responsible for limiting the space and resources in the bone marrow. We recently expanded our mathematical model of B-cell development to include the kinetics of antigen-experienced B cells to determine whether a feedback pathway affects B-cell development in aged mice. We suggest that comparing the differences in B-cell development between B-cell-depleted and control aged mice, using our mathematical model shown in Fig. 4.1, shows that the production of B lymphocytes increases in aged B-cell-depleted mice [paper in preparation].

4.4.2 Aging-Associated Changes in B-Cell Maturation and Homeostasis

In addition to changes in the quality and potential of lymphocyte-cell precursors, the homeostatic control of mature primary and antigen-experienced pools of cells displays a spectrum of age-associated changes. Many of these features are similar in humans and mice. Primary pools of naïve B cells "fill up" by young adulthood, and their size (total number of cells) and composition (BCR repertoire) are maintained by both new input from the bone marrow and competitive selective and homeostatic processes acting on the mature and antigen-experienced populations. Overall, about 90 % of developing B cells may be eliminated before they exit the bone marrow (Goodnow et al. 1995; Nemazee et al. 2000; Nossal 1994). Approximately two-thirds of newly emerging, transitional-stage B cells are lost by the negative selection of clones that produce autoreactive (i.e., acting against the body's own tissues) and polyreactive antibodies (i.e., acting against many self and foreign antigens).

Many aging-associated changes in primary B-cell production, selection, and maintenance have been documented. There is strong evidence in mice that many of

these cell-intrinsic changes, and the altered dynamics of the developing subset, reflect extrinsic changes in the B cells in the bone-marrow microenvironment. For example, the ability of bone-marrow stromal cells to release interleukin 7 (IL-7), a growth factor necessary for B-lymphocyte development, declines with age. These extrinsic changes in the bone-marrow microenvironment contribute to the dysregulation of early B-cell development during aging (Stephan et al. 1998). Furthermore, in aged mice, the size of the pre-B-cell subset and the pre-B to pro-B-cell throughput are reduced. Taken together, these changes cause a reduced transit through the bone-marrow developmental stages, resulting in a significantly lower output of B cells by the bone marrow in aged mice. Indeed, the bone-marrow B-cell output in aged mice eventually falls to about 10 % of that observed in young mice (Guerrettaz et al. 2008). The significant reduction in pre-B-cell numbers is sufficient to account for this decline. This is a consistent finding across several mouse strains. Despite these reductions in the potential B-cell lineage and shifts in the throughput and production of primary B cells, the overall numbers of B cells at the periphery remain relatively constant with age in mice (reviewed by Cancro and Allman 2005; Miller and Cancro 2007). Thus, the reduced input to the periphery is counterbalanced by the increased lifespans of mature B cells (Kline et al. 1999; Quinn et al. 2005), the homeostatic expansion of activated or antigen-experienced B cells (Johnson et al. 2002), and reduced repertoire diversity (Weksler 2000; Weksler et al. 2002). The picture in humans is less clear. Many analyses have been restricted to circulating subsets. However, although there are broad individual variations in mature B-cell numbers, both the proportion and number of total B cells decrease with age in humans (reviewed by Ademokun et al. 2010). This appears to include reductions in some or all memory subsets, although further analyses are clearly required (Ademokun et al. 2010; Breitbart et al. 2002; Colonna-Romano et al. 2009; Dunn-Walters and Ademokun 2010). Thus, the decline in B-cell production with aging is attributable to many different factors, rather than to a single cause.

We analyzed human B-lymphocyte subsets at the periphery in different age groups and found a reduction in the naïve B-cell subset with age ($P<0.05$), but no statistically significant differences in the different memory B-cell subsets (Fig. 4.2). However, in the oldest group, the standard deviations and hence the variability between patients in the population sizes of naïve ($CD19^+CD10^-CD21^+CD27^-$), resting memory ($CD19^+CD10^-CD21^+CD27^+$), and tissue-like memory B cells ($CD19^+CD10^-CD21^-CD27^+$) were higher than in the younger age groups ($P<0.01$, $P<0.05$, and $P<0.05$, respectively). This means that there is an age-related increase in the variation among individuals of the total number of experienced B cells (i.e., B-cell subpopulations that interacted with the antigens), so that different individuals may experience different degrees of decline in their immune function. The basis for this diversity is not yet known. However, the degree of individual variation suggests the involvement of changes in B-cell generation and selection in the bone marrow, although selective or homeostatic processes at the periphery may also be involved (Ademokun et al. 2010; Silva et al. 2011).

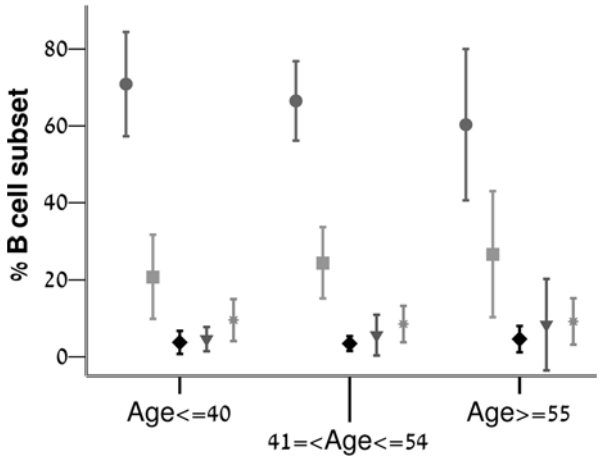

Fig. 4.2 Means and standard deviations of the proportions of B-cell subpopulations in human blood samples. We transformed the age variable to a group variable according to the age distribution of the participants. The participants were divided into three age categories: <41 years, 41–54 years, and >55 years old. Naïve B cells are represented in *circle*, resting memory in *square*, active memory in *diamond*, tissue-like memory in *triangle*, and transitional in *asterisk*

4.4.3 B-Cell Maintenance and Function with Aging

Studies conducted primarily in mouse models provide a relatively clear picture of the changes in the status of the B-cell compartment that occur during aging. Whereas the numbers of B cells in the peripheral lymphoid organs do not change significantly in old age, the distributions of functional subsets change with aging. Thus, B-cell populations become increasingly dominated by antigen-experienced cells specific for environmental and autoantigens (Breitbart et al. 2002, Cancro and Allman 2005). These B cells exhibit longer half-lives than naïve B cells, which are the primary B-cell constituents of the peripheral lymphoid organs of young animals. In mice, nearly 100 % of B cells in the spleen display an antigen-experienced receptor (Kline et al. 1999). This population shows greater diversity in specificity than the antigen-experienced and selected population that becomes more prominent in aged animals. Interestingly, the repertoire changes seen in aged humans are not synchronous, and the loss of diversity is associated with poor health status (Gibson et al. 2009).

4.4.4 Impaired Responses to Vaccination in Older Humans

Changes in antibody responses to vaccination ultimately involve B-cell function, and therefore tell us something about the status of the B-cell compartment. Perhaps the best-studied vaccine response is that to the influenza vaccine. Vaccination leads

to protective immunity in 65–80 % of young adults, but in only 30–50 % of elderly people (Remarque et al. 1998; Sasaki et al. 2011). In general, all vaccinated individuals show reduced antibodies to the virus. A recent study analyzed the antibody responses of young and older adults to inactivated influenza vaccine, and showed that 90 % of young adults responded to the vaccine by producing neutralizing antibodies, whereas only 57 % of older adults responded (Sasaki et al. 2011). The older adults produced fewer serum antibodies capable of blocking viral hemagglutinin (Sasaki et al. 2011). Neutralizing antibodies against hemagglutinin prevent viral entry into the cells. B cells from aged individuals produced significantly fewer antibodies than did those from young adults, and these antibodies were relatively ineffective in neutralizing the virus (Sasaki et al. 2011).

Although memory B cells are maintained in old individuals, they may be fewer in number, hyporesponsive to antigen-induced activation, less capable of clonal expansion, and/or less capable of differentiation into antibody-secreting cells (ASC) than those of younger people (Sasaki et al. 2011). It is noteworthy that equivalent amounts of antibodies are secreted by single ASCs from aged and young vaccinees (Sasaki et al. 2011). Thus, once formed, the ASCs are equally functional.

The responsive memory B cells in the aged cohort were generated much earlier in life, suggesting that the B-cell memory of pathogen strains to which the individuals were exposed later in life was poorer than memory of antigens that were encountered in young individuals. This may indicate a relative deficit in the ability of older people to mount primary responses to completely new antigens or to improve the affinity of existing memory cells for new modified viruses.

A key study assessed the ability of older people to mount primary antibody responses, which derive from naïve B cells (Dunn-Walters et al. 2003). Older humans mounted delayed neutralizing antibody responses and had very significantly elevated levels of virus in the bloodstream for the first 10 days after vaccination. However, the antibody titers of aged and young individuals were equivalent to 28 days after immunization. This early deficit may be attributable to the reduced repertoire diversity in the responding naïve B-cell pool. Fewer antibody-secreting-cell precursors and/or cells with lower average affinity may have been recruited into the response, causing a lag in neutralizing antibody production, which was later compensated by the clonal expansion of the B cells.

We used our computational method to evaluate the antibody repertoire diversity after vaccination in old and young people (data taken from Ademokun et al. 2011) to determine whether repertoire diversity is reduced in elderly people. Figure 4.3 shows that in the young group (aged 18–49 years), the baseline mean antibody repertoire diversity (before vaccination) was significantly higher than that in the old group (aged 65–89 years). Furthermore, seven days after vaccination, at the peak of the antibody response, the diversity decreased very sharply in the young group, but only moderately in the old group. The decline in diversity in young adults results from the increasing levels of vaccination-specific antibodies. Therefore, in older people, vaccination seems less effective in producing vaccination-specific antibodies. In the young group, the mean diversity returned to the baseline level by 28 days after vaccination, whereas in the old group, the mean diversity remained low.

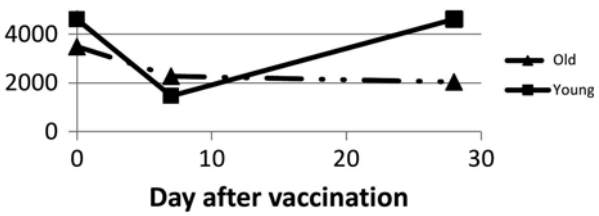

Fig. 4.3 Antibody repertoire diversity after vaccination. Diversity is expressed as number equivalents (Jost 2007), which reflect the number of equally sized antibody clones required to produce a given diversity value

4.5 Conclusion

We are finally starting to understand the effects of aging on the immune system, in particular on the population dynamics, repertoire diversity, and functions of B lymphocytes. This understanding has been facilitated by the development of mathematical models and statistical approaches that allow sophisticated data analyses. However, more research is required if we are to make the best use of these methods and fully understand the changes that B cells—and other parts of the immune system—undergo during aging. Research into the aging immune system will benefit from the collection of kinetic data for B lymphocytes, in terms of their development, activation, antigen exposure, etc., from numerous patients in different age groups. These findings will advance the development of technologies that can enhance human immunoresponsiveness during aging. This is of major importance to the aging global population and may constitute a breakthrough in practical medicine and basic immunology. This will significantly improve the quality of life and healthspans of older adults.

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Chapter 5
How the Aging Process Affects Our Immune System: Mechanisms, Consequences, and Perspectives for Intervention

Dietmar Herndler-Brandstetter

5.1 Introduction

Our body relies on a set of highly specialized immune cells (Fig. 5.1) that are able to perform a multitude of tasks and help us to survive a wide variety of infectious diseases and to establish memory immune cells to prevent reinfection with the same pathogens. Depending on the mechanism they use to recognize pathogens, immune cells belong to either the innate or the adaptive branch of the immune system. Innate immune cells, such as phagocytic cells and natural killer cells, recognize pathogen-associated molecular patterns, which are characteristically expressed by a broad spectrum of microorganisms. In contrast, adaptive immune cells, such as T and B lymphocytes, have been educated in the bone marrow or the thymus to discriminate between self and nonself. T and B lymphocytes are an important part of the immunosurveillance machinery, as they continuously scan the surface of cells in our body and are able to identify cells that have been infected by viruses and intracellular bacteria. This is made possible because all proteins that are synthesized in the cell, including proteins made during viral and bacterial replication, are routinely being chopped into small pieces, so-called peptide epitopes or antigens, by cylindrical organelles named proteasomes and presented on the cell surface. Upon encounter of such antigens presented on the surface of infected host cells, T and B lymphocytes undergo a dramatic numeric expansion in the lymph nodes and differentiate into effector T lymphocytes and plasmablasts (Fig. 5.2). Effector lymphocytes and plasmablasts are highly specific and execute effector function, such as killing pathogen-infected host cells and producing antibodies that label pathogens to be killed by phagocytic cells.

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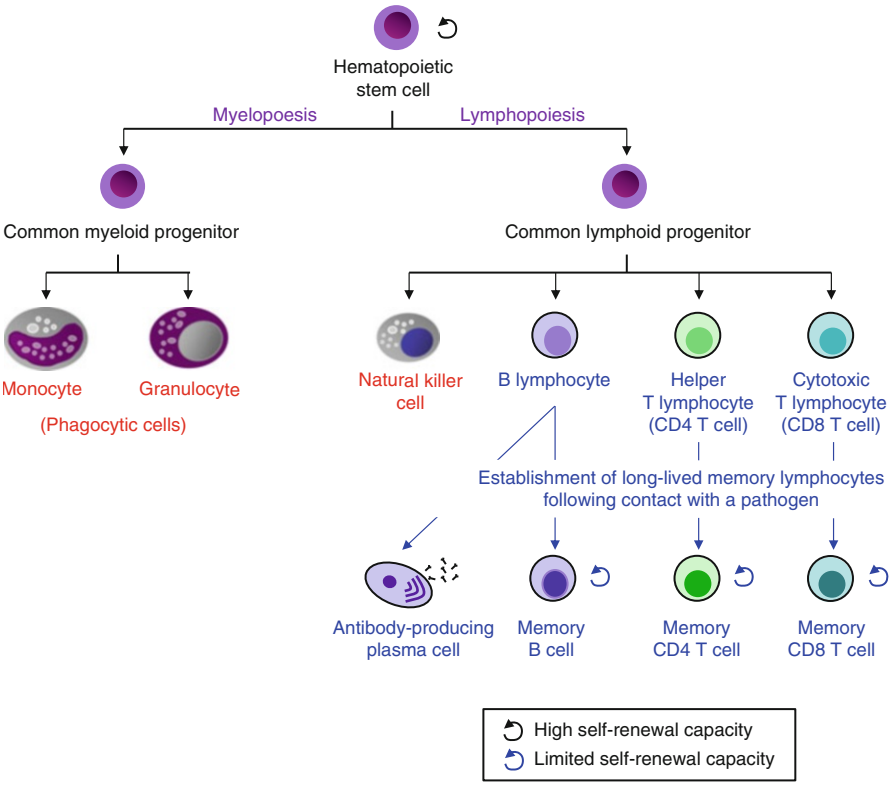

Fig. 5.1 A simplified overview of human immune cell development. Self-renewing hematopoietic stem cells (HSC) reside in the bone marrow and give rise to all blood cells, such as the myeloid (monocytes, macrophages, dendritic cells, granulocytes) and lymphoid lineage (natural killer cells, T and B lymphocytes). Innate immune cells are highlighted in *red*, while adaptive immune cells are labeled in *blue*

After resolution of the infection, most of the effector cells die. However, a substantial population of pathogen-specific, long-lived memory T lymphocytes and plasma cells forms. These memory immune cells are long-lived, respond to the pathogen much faster than naïve cells, and produce higher amounts of pathogen-specific antibodies and effector immune cells. The adaptive arm of our immune system is therefore able to "remember" previously encountered pathogens, and the memory immune cells established during a primary immune response are able to prevent recurrent infections with the same pathogen. The same principle is used in the case of vaccinations, where noninfectious parts of pathogens are used to establish memory immune cells. Yet, all the immune cells mentioned above are affected by the aging process, although adaptive immune cells are more dramatically affected than innate immune cells (Shaw et al. 2013; Linton and Dorshkind 2004). This book chapter will therefore focus on the mechanisms and consequences of adaptive immune aging, with a particular spotlight on T lymphocytes.

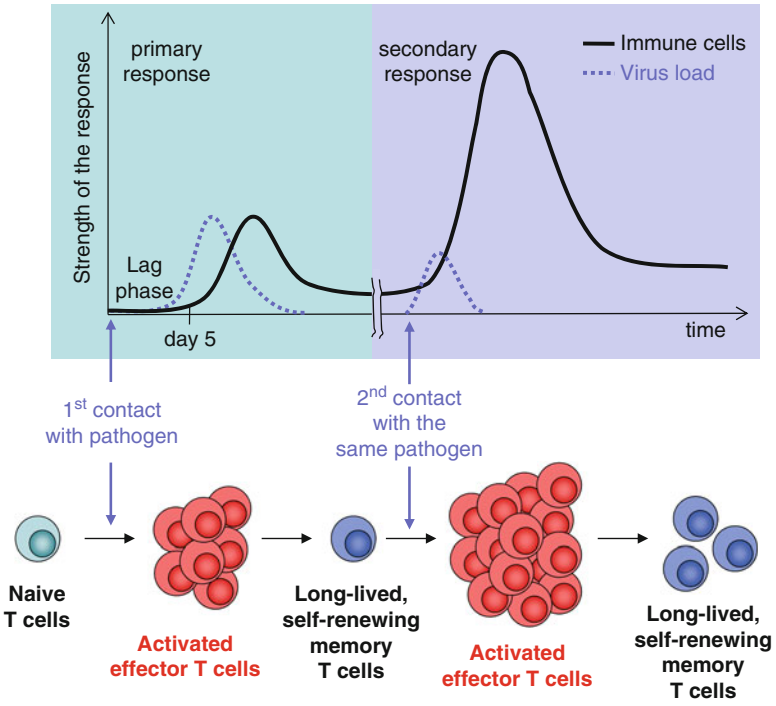

Fig. 5.2 Schematic representation of a primary and secondary immune response, the hallmark of adaptive immunity. Upon first contact with a pathogen, innate immune cells phagocytize the pathogen and present fragments of the pathogen (called "antigen") on their surface to adaptive immune cells, such as T lymphocytes. Naïve T lymphocytes with the highest specificity to the antigen are activated by the innate immune cells and undergo a massive expansion in the lymph nodes and become activated effector T lymphocytes that are able to leave the lymph nodes and migrate to the site of infection and clear the pathogen. Upon clearance of the pathogen, most of the activated effector T lymphocytes die, while a long-lived, self-renewing memory T-lymphocyte pool forms

5.2 How Aging Affects Immune Cell Generation and Function

The age-dependent decline in immune system function is determined by genetic and environmental factors and is caused by the age-dependent exhaustion of hematopoietic stem cells (HSCs), a progressive decline in the amount of functional tissues that generate immune cells, and the accumulation of "aged," dysfunctional immune cells as a result of decreased immune cell renewal as well as certain persistent infections.

Clinically, aging is associated with a higher prevalence of respiratory tract infections (influenza and pneumonia), urinary tract infections, skin and soft tissue infections, infective endocarditis, bacterial meningitis, tuberculosis, and herpes zoster (shingles). Yet, these infections are not only more frequent but also more severe in older adults and have distinct features with respect to clinical presentation (Gavazzi and Krause 2002). Old individuals may also fail to respond sufficiently to therapy and frequently suffer from opportunistic infections, recurrent infections with the

same pathogen, or reactivation of latent infectious diseases, such as those caused by mycobacterium tuberculosis and varicella zoster virus.

The implementation of immunizations in the twentieth century has been a great medical success, and vaccinations are considered the most cost-effective medical procedure in preventing morbidity and mortality caused by infectious diseases, though no vaccines are yet available for a number of pathogens that frequently affect older adults. And existing vaccines frequently do not induce sufficient protection (Grubeck-Loebenstein et al. 1998; Herndler-Brandstetter et al. 2006). For example, the efficacy of a herpes zoster vaccine is 64 % in persons aged 60–69 years, but it is only 18 % in persons aged 80 years and older (Oxman et al. 2005). Similarly, the efficacy of influenza vaccines in persons aged 65–74 years is only around 55 % and drops to 30 % in persons aged 75 years and above (Goodwin et al. 2006). The reduced vaccine efficacy is due to low levels of immunoglobulin G (IgG) antibodies, delayed peak antibody titers, and shortened maintenance of titers after vaccination. Due to their less diverse immune cell repertoire, older persons have a particularly impaired immune response to pathogens with which they have not been in contact previously, such as newly emerging influenza virus strains. As a consequence, influenza and pneumonia are still ranked among the ten major causes of deaths in people aged 65 years and over in developed countries. An important goal therefore remains, namely, to develop new vaccines that are able to confer sufficient and long-lasting protective immunity in older people.

Many organs with a high cell turnover, such as the skin and blood, comprise short-lived cells that require continuous replenishment by somatic stem cells. Aging results in the inability of these tissues to maintain homeostasis, and it is believed that somatic stem cell aging is one contributing factor. The accumulation of DNA damage and an age-related deficiency in DNA damage repair have been shown to limit HSC renewal in the bone marrow (Rossi et al. 2007). Aged HSC also have a decreased capacity to differentiate into committed lymphoid progenitor cells (Rossi et al. 2005; Florian et al. 2013), thereby contributing to the decreased generation of new, naïve T and B lymphocytes in older adults (Fig. 5.1). The remainder of this chapter will focus on evidence concerning aging-related changes in T-lymphocyte development and implications for interventions (for a review of current knowledge on aging-related changes in B-cell function, see Shahaf et al. 2014).

5.2.1 Naïve T Lymphocytes and Aging

The most dramatic impact on the generation of new, functional naïve T lymphocytes is the age-dependent shrinkage of the thymus gland (Fig. 5.3).

Already at 1 year of age, functional thymic tissue (cortex and medulla) starts to decline while adipose tissue increases during aging, with only about 10 % functional thymic tissue left at the age of 50 (Steinmann et al. 1985; Palmer 2013). As a consequence, the thymic output of the newly produced naïve T lymphocytes decreases leading to a dramatically reduced number and diversity of naïve T lymphocytes in old age (Table 5.1 and Fig. 5.4). The decrease in naïve T-lymphocyte number and

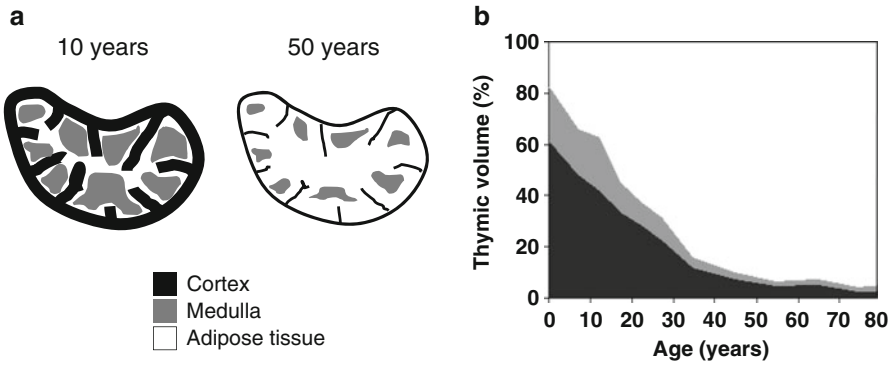

Fig. 5.3 Schematic representation of the age-dependent involution of the human thymus. (**a**) During aging, thymic cortex (*black*) and medulla (*gray*) are reduced in size while adipose tissue (*white*) is increased. The diagram in (**b**) is based on data published by Steinmann et al. (1985)

Table 5.1 Age-related changes within the adaptive immune system

Immune cell type	Age-dependent alterations	References
T lymphocytes	↓number and function of naïve T lymphocytes	Fagnoni et al. (2000); Haynes et al. (1999); Lazuardi et al. (2005)
	↑number of highly differentiated effector memory T lymphocytes	Almanzar et al. (2005)
	↓expression of co-stimulatory molecules (CD28, CD27, CD40L)	Effros et al. (2003)
	↑expression of senescence-associated molecules (CD57, KLRG1)	Brenchley et al. (2003)
	↑number of T lymphocytes producing the pro-inflammatory cytokine interferon γ	Zanni et al. (2003); Almanzar et al. (2005); Kovaiou et al. (2005)
	↓proliferative capacity due to shorter telomeres and lower telomerase levels	(Effros et al. (2003)
	↓DNA damage repair	Brunner et al. (2012)
B lymphocytes	↓size and number of germinal centers in lymph nodes	Lazuardi et al. (2005); Mattila and Tarkkanen (1997)
	↓antibody affinity (shift from IgG to IgM)	Johnson and Cambier (2004)
	↓serum antibodies specific for foreign antigens	Weksler and Szabo (2000)
	↑serum antibodies specific for self-antigens	LeMaoult et al. (1997)
	↓stimulation by follicular dendritic cells	Aydar et al. (2002)
	↓expression of co-stimulatory molecules (CD27, CD40L)	Colonna-Romano et al. (2003)

IgG immunoglobulin G, *KLRG1* killer cell lectin-like receptor G1, ↑ increase, ↓ decrease

diversity is believed to be the major driving factor for several clinical complications observed in older adults (Saurwein-Teissl et al. 2002; Goronzy et al. 2013; Johnson and Cambier 2004; Weyand et al. 2009), and this hypothesis is further supported by

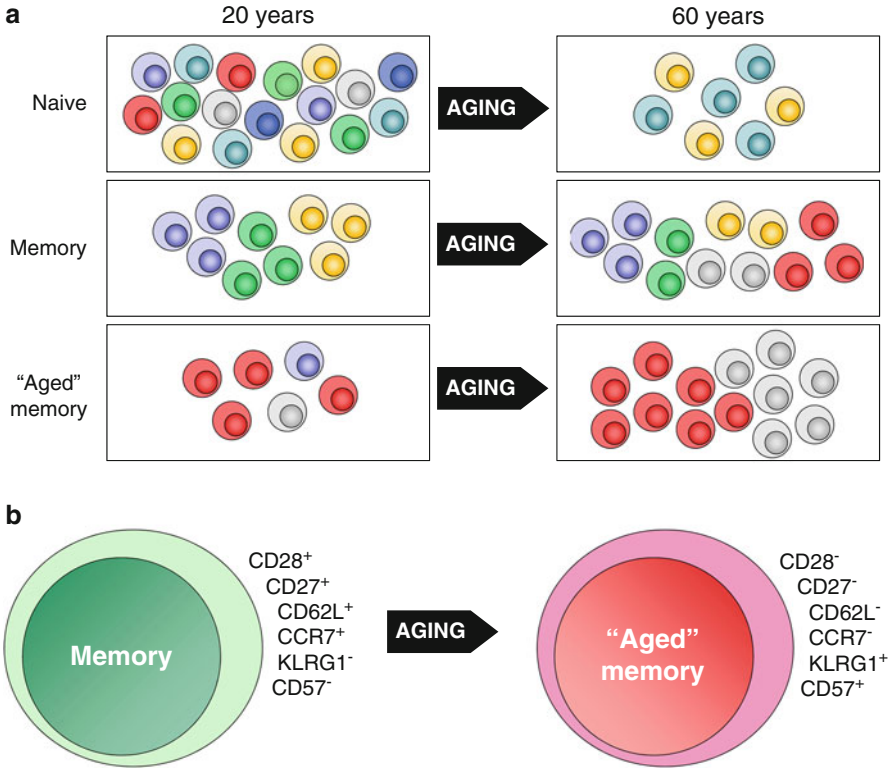

Fig. 5.4 The impact of aging on naïve and memory T-lymphocyte diversity (**a**) and memory phenotype in humans (**b**). The different colors indicate T lymphocyte with distinct pathogen specificity. *CCR7* C–C chemokine receptor type 7, *CD* cluster of differentiation, *KLRG1* killer cell lectin-like receptor subfamily G member 1; + indicates the expression of a respective molecule while – indicates its absence

proof-of-concept experiments in animals (Yager et al. 2008; Haynes and Swain 2012; Sakaguchi et al. 2003). Firstly, a decrease in naïve T- and B-cell number and diversity is associated with an impaired primary T-lymphocyte and antibody response (Sauce and Appay 2011; Goronzy and Weyand 2013). Secondly, a decreased naïve T-lymphocyte output imposes a proliferative pressure on the remaining naïve T lymphocyte to maintain their cell numbers. This induces a peripheral selection process of naïve T lymphocyte that have a high reactivity to self-antigens.

These skewed naïve T lymphocytes, together with deficiencies in maintaining telomeres and overall DNA stability, genetic risk factors, and an increased pro-inflammatory background, are believed to be the cause for the age-dependent increase in autoimmune disorders, such as rheumatoid arthritis, arteriosclerosis, and osteoarthritis (Goronzy et al. 2013). The same factors may also contribute to an impaired immunosurveillance and a decreased ability of "aged" immune cells to destroy cancer cells in older persons (Finkel et al. 2007; Hazeldine et al. 2012). Yet, people

aged 65 years and older do not only have a tenfold higher cancer incidence rate than people younger than 65 years (Muss 2009), but their pro-inflammatory milieu might further predispose those older patients that receive targeted cancer immunotherapy to immune-mediated toxicity (Bouchlaka et al. 2013).

But thymic output and peripheral homeostatic proliferation are not the sole factors that determine the size and diversity of the naïve T-lymphocyte pool in old age. Persistent, life-long infection with the cytomegalovirus (CMV), but not Epstein-Barr virus or varicella zoster virus, leads to an accelerate decline of naïve T lymphocytes and facilitates the accumulation of "aged" CMV-specific memory T lymphocytes (Almanzar et al. 2005; Weinberger et al. 2007).

In addition to the age-dependent decrease in naïve T-lymphocyte number and diversity, "aged" naïve T lymphocytes have shorter telomeres and have therefore a decreased capacity to undergo extensive clonal expansion upon encounter with a novel pathogen. The shortened telomeres are a result of the age-related increase in peripheral naïve T-lymphocyte proliferation, a desperate attempt of the organism to maintain peripheral naïve T-lymphocyte numbers in the face of declining thymic naïve T-lymphocyte output.

Another important aspect relates to the phenotypic differences between naïve T lymphocytes in young and older persons. Homeostatic proliferation has been shown to induce characteristic phenotypic changes, and naïve T lymphocytes with high affinity to self-antigen undergo faster rates of homeostatic proliferation and preferentially acquire a "memory-like" phenotype (Rudd et al. 2011; Murali-Krishna and Ahmed 2000). Moreover, naïve T lymphocytes express interleukin-6 receptor alpha (IL-6Rα) and IL-7Rα at a lower frequency (Pfister et al. 2006; Herndler-Brandstetter et al. 2011; Alves et al. 2007). These studies accentuate an important problem that has not received much attention. How reliable are surface markers, such as the lymph node homing markers CD62L and CCR7, the co-stimulatory molecules CD27 and CD28, and the signal strength-modulating molecule CD45RA, in identifying aged human naïve T lymphocytes? Although studies in mice have demonstrated that naïve T lymphocytes that undergo extended homeostatic proliferation can acquire a memory-like phenotype, data in humans are very limited. Circumstantial evidence is provided by one study, which identified a characteristic memory-like T-lymphocyte population in healthy, CMV-seronegative older persons who characteristically still had a good immune response following influenza vaccination (Schwaiger et al. 2003; Herndler-Brandstetter et al. 2005). These novel memory-like T lymphocytes had a highly diverse repertoire, long telomeres, and produced large amounts of IL-2, and may therefore represent homeostatically expanded naïve T lymphocytes (Herndler-Brandstetter et al. 2008).

In conclusion, the number and diversity of naïve T and B lymphocytes dramatically declines during aging, and circumstantial evidence indicates that this may reduce the capacity to mount protective immune responses to novel vaccinations and newly emerging pathogens. However, there are still no large-scale studies published that have evaluated whether high numbers of naïve T lymphocytes, a diverse T lymphocyte repertoire, intact IL-2 production, and other naïve T lymphocyte parameters correlate with an intact immune responsiveness following vaccination

with neoantigens in older persons or whether such older individuals have a decreased risk of influenza-associated morbidity and mortality. The design of such studies is further complicated by the fact that the phenotypic markers used to identify naïve T lymphocytes in young persons may not accurately discriminate between functionally naïve and "aged" naïve T lymphocytes in older adults.

5.2.2 Memory T Lymphocytes and Aging

The ability to generate and maintain functional memory T lymphocytes following infection or vaccination is a hallmark of adaptive immunity and ensures protection upon recurrent infections. In old mice, the generation of functional, long-lived memory T lymphocytes is impaired, which has been attributed to functional defects in naïve T-lymphocyte stimulation, decreased effector T-lymphocyte expansion, and migration (Haynes et al. 2003; Kapasi et al. 2002). In addition, the aged microenvironment may limit the number and quality of niche cells that are responsible for maintaining the long-term survival of memory T lymphocytes. In humans, memory T lymphocytes are also affected by the aging process, although to a lesser extent than naïve T lymphocytes. For example, CMV-specific T-lymphocyte immunity seems to be maintained during aging, as overt CMV disease is rare in older persons (Cicin-Sain et al. 2011; Rafailidis et al. 2008). Yet, herpes zoster, which is caused by the reactivation of the varicella zoster virus that causes chickenpox in children, occurs more frequently in older adults. Several studies also demonstrated that booster vaccinations in older persons lead to decreased IgG antibody concentrations, delayed peak antibody titers, and a more rapid decline in antibody titers (Weinberger et al. 2008). But intrinsic defects in T lymphocytes are not always to blame. That is to say, decreased synthesis of tumor necrosis factor alpha (TNF-α) by phagocytes restricts cutaneous immunosurveillance by memory T lymphocytes during aging, providing an explanation for the increased susceptibility to cutaneous infections and malignancies in older individuals (Agius et al. 2009). In summary, these studies indicate that memory T lymphocytes, as well as their interaction with B lymphocytes and antigen-presenting cells, are less efficient in old age.

In humans, two major memory T-lymphocyte subsets can be distinguished based on their phenotypic and functional characteristics: central memory T lymphocytes with a $CD45RO^+$ $CD62L^+$ $CCR7^+$ $CD28^+$ $CD27^+$ phenotype reside mainly in the lymph node, while effector memory T lymphocytes with a $CD45RO^+$ $CD62L^-$ $CCR7^-$ $CD28^+$ $CD27^+$ phenotype circulate in the periphery. During aging, the frequency of effector memory T lymphocytes and highly differentiated "aged" $CD28^-$ memory T lymphocytes increases in the peripheral blood and bone marrow (Almanzar et al. 2005; Herndler-Brandstetter et al. 2012; Kovaiou et al. 2005) (Fig. 5.4). The accumulation of highly differentiated "aged" $CD28^-$ memory T lymphocytes, which have a highly restricted diversity, short telomeres, and a decreased responsiveness to antigenic stimulation, has been included in a set

of parameters defining the immune risk phenotype and correlates with a lack of antibody production after influenza vaccination in older persons (Olsson et al. 2000; Saurwein-Teissl et al. 2002). The loss of the co-stimulatory molecule CD28 and the corresponding age-dependent accumulation of $CD28^-$ T lymphocytes can be attributed to two mechanisms: repeated antigenic stimulation and IL-15-mediated homeostatic proliferation (Valenzuela and Effros 2002; Almanzar et al. 2005; Chiu et al. 2006).

In conclusion, although several human memory T-lymphocyte subsets have been identified, we still lack information about their survival, functional, and migratory properties in old age. The identification of the different microenvironmental niches and factors that maintain distinct memory T-lymphocyte subsets, in particular $CD28^-$ T lymphocytes, would expedite the search for novel markers that are able to distinguish homeostasis from repeated antigen-driven memory T lymphocytes.

5.3 The Need to Identify a Robust Set of Biomarkers of Human Immune Cell Aging

Although considerable progress has been made to identify the cellular and molecular mechanisms of immune cell aging, we still lack robust biomarkers that have been validated in large populations and that correlate with functional immune responsiveness and clinical parameters. The availability of a valid set of biomarkers will be of utmost importance to improve medical and preventive treatments in older adults and to evaluate potential therapies that aim to delay immunological aging.

Age-related changes within the human T-lymphocyte pool have almost exclusively been studied in cells derived from the peripheral blood. Yet, the peripheral blood contains only 2 % of the total body T-lymphocyte pool (Di Rosa and Pabst 2005). Only limited data are available on how aging affects naïve and memory T lymphocytes in lymphoid and extra-lymphoid organs (Sathaliyawala et al. 2013; Herndler-Brandstetter et al. 2012; Lazuardi et al. 2005). A prerequisite for defining biomarkers of human immune aging and testing strategies to reverse or delay immunological aging is to analyze naïve and memory T-lymphocyte populations in different organs and validate their phenotypic and functional characteristics. The impact of aging on T lymphocytes in distinct microenvironmental niches would also help us to, e.g., identify phenotypic and functionally distinct subpopulations of $CD28^-$ memory T lymphocytes that may have been generated by either chronic antigenic stimulation or life-long homeostatic proliferation. The functional analysis of aged human naïve and memory T-lymphocyte subsets in vivo, e.g., in humanized mice, may be another promising strategy to enhance our understanding about human T-lymphocyte aging (Rongvaux et al. 2013). Large-scale integrated projects that aim to define biomarkers of aging, such as the EU-funded project MARK-AGE, are also underway and may pave the way for personalized medical treatment and preventive interventions in older adults.

5.4 Developing Strategies to Delay Immunological Aging

The age-related involution of the thymus is the most important event that contributes to the aging of the adaptive immune system. Thymic reconstitution would therefore be a promising approach to prevent the decline of naïve T-lymphocyte output and the accumulation of highly differentiated, pro-inflammatory $CD28^-$ memory T lymphocytes. IL-7, IL-15, growth hormone, insulin-like growth factor 1, keratinocyte growth factor, ghrelin, and the ablation of sex steroids have all been shown to be important for thymopoiesis and could be used for therapeutic thymus restoration (Lynch et al. 2009; Dixit et al. 2007; Holland and van den Brink 2009; Aspinall and Mitchell 2008). For example, IL-7 treatment of old rhesus macaques increased the number of naïve T lymphocytes and improved the response to influenza vaccination (Aspinall et al. 2007). Although the use of hormones and cytokines to enhance thymopoiesis has yielded promising results in animals, side effects, continuous treatment, and cost-effectiveness may limit this approach in humans. Of great interest will be how the progress in the field of thymus and stem cell biology will be applicable for the reconstitution of thymic tissue in old age (Surani and McLaren 2006; Haynes et al. 2000).

It has also been shown that obesity accelerates thymic aging while caloric restriction inhibits thymic adipogenesis and thereby reduces the age-related involution of the thymus (Yang et al. 2009a, b). For example, caloric restriction initiated in early adulthood in nonhuman primates was shown to improve the maintenance and/or production of naïve T lymphocytes and consequently preserved T-lymphocyte diversity (Messaoudi et al. 2006). Caloric restriction also improved T-lymphocyte function and reduced the production of inflammatory cytokines.

The prevention of life-long stimulation of the immune system by chronic bacterial and viral infections, especially CMV, seems to be the most promising strategy. Early childhood vaccination against CMV might be one option to prevent CMV infection and CMV-associated acceleration of immunosenescence. Although no CMV vaccines are yet available on the market, several CMV vaccine candidates are being tested in clinical trials.

Another strategy to reverse immunosenescence would be the depletion of "aged" $CD28^-$ memory T lymphocytes. Recent studies have shown that the same clonotypes occur in both, central memory T lymphocytes and "aged" $CD28^-$ memory T lymphocytes, indicating that unique T-lymphocyte specificities may not be lost following depletion of $CD28^-$ T lymphocytes (Weinberger et al. 2009; Iancu et al. 2009). However, $CD28^-$ memory T lymphocytes may be important for tissue-mediated immunity, and due to their lack of lymph node homing markers, these cells are likely to occupy different niches than naïve and central memory T lymphocytes (Remmerswaal et al. 2012). Moreover, a sudden drop of T-lymphocyte numbers due to depletion of $CD28^-$ memory T lymphocytes may lead to increased peripheral naïve T-lymphocyte proliferation and exhaustion.

Aging is also associated with a decreased efficacy of vaccinations (Chen et al. 2009). Improved vaccination strategies, new adjuvants, alternative routes of administration,

and new vaccines that specifically target the aged immune system could help to ensure a better protection and decrease morbidity and mortality caused by infectious diseases in the older population (Kovaiou et al. 2007; McElhaney 2009). Because the aging process varies widely among individuals, it will be important to identify those persons who would benefit most from immunomodulatory treatments by using biomarkers of immune cell aging. As mentioned above, a set of valid biomarkers will be a prerequisite to assess any benefit of a potential therapy that aims to delay immune cell aging.

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Chapter 6
A Conflict of Interpretations in Gerontology

Hans-Jörg Ehni

6.1 Introduction

Gerontology is a special member of the family of sciences. While researchers from other fields are encouraged to seek interdisciplinary cooperation, gerontology is itself interdisciplinary by its very nature and subject. The corresponding variety of perspectives and methods is perfectly necessary and appropriate, as *aging* and *old age* are phenomena which have many different facets ranging from the molecular level of the human body over multiple aspects of the experience of being an older member of a society to the institutional frame of such experiences. The term "old age" is used here to refer to the life stage where biological and psychological aging processes have manifested themselves. Regarding the multiplicity of perspectives, this internal interdisciplinarity of gerontology is not just an asset. It also creates many challenges in the integration of a multitude of methodological and conceptual perspectives, which are not easily merged into one big picture of aging. Indeed, a possible divide between the natural sciences on the one hand, and the social sciences and humanities on the other hand separates the different areas of the field of gerontology. Such a divide may generate conflicts and a lack of mutual understanding between the natural and the social sciences which both explore the phenomenon of aging. This may be attributed to *two cultures*, which lack a proper mutual understanding and common goal, according to the concept coined by the scientist and novelist Charles P. Snow in his speech and later book on *The Two Cultures and the Scientific Revolution*. Snow assumed the common culture of the humanities to be oriented towards the past and directed against the rationality of the natural sciences (Snow 1959).

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While this perspective on the humanities is at least debatable, fundamental differences of theories and methods may be more obvious. For some, physics may be the ideal science, developing value-free and quantifiable natural laws, which are based on empirical observations and experiments, and could also be put to scrutiny by the test of falsification. This is expressed in the belief of physicalism, that at some point in the future the scientific description of all phenomena in the world will be reducible to the language of physics (see, for instance, Stoljar 2009). The success of the natural sciences and their technological success may seem to support such a claim. However, not everybody may be convinced that this will be possible. For them, the realms of symbolic meaning, morality, and social phenomena require their own qualitative methods and theory in order to develop an adequate understanding. In turn, from their perspective, the scientific quest for knowledge appears to be less objective and indeed value-laden due to its social context. It is easy to see how both perspectives on scientific knowledge can come into conflict and generate a divide between the humanities/social sciences and the natural sciences as has happened in the German "Positivismusstreit," the so-called positivism dispute between the neo-Marxist School of Frankfurt represented by Theodor W. Adorno and Jürgen Habermas and the school of Karl Popper (Zuidervaart 2011).

This chapter proposes that in gerontology, there is indeed a comparable conflict and divide of *two cultures* between research agendas and, consequently, between representatives of biogerontology and social gerontology. This conflict becomes apparent in different interpretations of aging, results in mutual attacks, and has the potential to hinder the necessary cooperation among the different disciplines of gerontology. It will be argued that these quarrels originate mainly from different principal practical goals, which guide the research agenda in biogerontology or social gerontology and also partially guide their respective interpretation of aging. The respective debate is therefore called a *conflict of interpretations*, a term which is borrowed from the French philosopher Paul Ricœur, however, without the claim to use it exactly in the same sense as he does (Ricœur 1974, orig. Ricœur 1969).

As gerontology is commonly understood as the basic science of aging and as a mainly theoretical field of scientific inquiry, it may come as a surprise that two of its most important disciplines should have predominant practical goals. But from the self-characterization of important representatives of each field as expressed in textbooks, programmatic articles, and handbooks, this role of practical goals beyond the mere theoretical preoccupation with aging becomes quite obvious. The more detailed discussion of these goals in Sects. 6.2 and 6.3 will show that practical goals are a crucial component of the self-understanding and basic definitions of each discipline. In biogerontology, the predominant practical goal is the prevention and treatment of age-associated diseases. In contrast, the primary goal of social gerontology is the fight against age discrimination and ageism. In both cases, the practical goals are based on basic assumptions about the aging process and old age.

The starting point for biogerontology is the definition of aging as a degenerative process (or the sum of such processes), which in turn leads to a research focus on the connection between aging and disease. A typical example may be a laboratory

experiment with different organisms to understand how caloric restriction affects their aging processes, their longevity, and physiological functions. The next step to such experiments is to perform clinical trials, in which some researchers have started to test caloric restriction leads to similar effects in humans (see, e.g., Fontana 2009). As opposed to that, social gerontology is guided by the discovery of structural age discrimination and negative attitudes towards older people, which are based on influential negative cultural stereotypes, such as convictions that older people show many psychological or moral defects, for instance, they are not creative, inflexible, not able to learn something new, and, at the same time, they are stubborn, backward oriented, righteous, avaricious, and so on (Palmore et al. 2005). From this discovery results the emancipatory task of social science research in gerontology to unmask such stereotypes and discriminatory social structures. These conflicting goals do not only guide the research agendas in each field but also the interpretation of aging itself and which phenomena are considered to be part of the respective aging processes and the life course. Both interpretations include evaluative, normative elements on which the practical goals are based. On the one hand, the connection between processes of aging and disease leads to negative evaluation of aspects of aging in biogerontology. On the other hand, social gerontologists, who are concerned with the influence of negative stereotypes of old age, stress the positive aspects of aging and confirm old age as an important part of the life course.

These different evaluations of aging and old age are at the core of the conflict between biogerontological and sociogerontological interpretations of aging, which are presented in more detail in the second and third sections. This conflict, which partially results from the methodological and theoretical divide between the social sciences/humanities and the natural sciences, will be explained in more detail in Sect. 6.4. It becomes visible in mutual accusations such as an alleged ageism of the natural sciences, put forward by some social gerontologists, and in the criticism of an overly optimistic conception of aging, which some biogerontologists see expressed in concepts such as successful aging. Section 6.5 then outlines the possible problems resulting from this conflict. These problems are not merely theoretical. As the conflict is closely linked to practical goals, it is not only about interpretations but also about the future of aging research and how this future should be shaped by one or both research agendas. What started as a conflict of the interpretation of aging continues as one on its ethical meaning and becomes a struggle for influence and research budgets. Facing the challenges of population aging, this is unfortunate as it may draw a confusing picture of the field and also lead to a mere confrontation of opposed views instead of a necessary complementary perspective on aging. In order to show the necessity for complementing each of the perspectives, Sect. 6.5 also identifies some shortcomings and limits of each perspective as well as resulting problems. Finally, Sect. 6.6 presents a possible way out of the conflict. An interdisciplinary dialogue based on these common themes would be necessary to overcome the conflict, which needs not to be solved completely but requires a better mutual understanding, which may still lead to a conflict, although to a better informed one at least.

6.2 Biogerontology: Preventing Age-Associated Diseases

In many statements of prominent biogerontologists, the main practical goal of the discipline is mentioned in close connection with its very definition. Examples are Robert Arking's textbook *The Biology of Aging* or David Gems' statements on the ethics of interventions into aging (Arking 2006; Gems 2003). Consequently, biogerontology is the basic science of biological aging processes with the objective to find methods to prevent and treat age-related diseases (Gems 2011). This practical goal is crucial for biogerontologists' self-understanding and their conception of aging. It connects basic research questions, definitions of aging, the evaluation of aging processes and old age, and research agendas.

For David Gems the most critical question for biogerontology is how aging leads to disease (Gems 2011). In more general terms, the practical goal of preventing and treating age-related diseases by means of intervening in aging processes relies on the assumption that there is a direct or indirect connection between aging and disease. At the moment, this connection is still open to debate in biogerontology. The different positions become apparent in the terminology, when biogerontologists either refer to "age-related" or "age-associated diseases." "Age-related" reflects the stronger assumption that there is a causal connection. David Gems even goes one step further and confirms that aging itself should be considered a disease and that biogerontological findings allow no other definition. Others, however, are more careful. Leonard Hayflick defends the position that aging only increases vulnerability to diseases but cannot be considered a disease itself (Hayflick 2004). This would correspond to the concept of "age-associated diseases," implying that there is some coincidence between aging and particular diseases, but not necessarily a causal connection between both. An alternative explanation would be that the incidence of some diseases typical for old age increase with a prolonged exposure to risk factors over time (Blumenthal 2003). A middle ground is taken by Thomas Kirkwood, who sees a common causal pathway in some phenomena of aging and some diseases although they may not be completely identical. "Given that ageing is driven by damage, and that this is also true for many age-associated diseases, there is likely to be considerable overlap between the underlying causative pathways" (Kirkwood 2011, p. 67).

However, no matter how the relation between aging and disease is conceived, it is important to draw the attention to the first proposition in Kirkwood's statement: "…ageing is driven by damage…." This points to a basic understanding of aging in biogerontology, which equals it to damage, degeneration, and dysfunction. This understanding can be found in Kirkwood's own definition that aging is the accumulation of non-repaired cellular and molecular damage beyond the evolved limits of the body's repair mechanisms (Kirkwood 2005, p. 438). In an attempt to summarize the fundaments of biogerontological knowledge, Suresh Rattan calls this basic assumption of biogerontology its "mechanistic principle" (Rattan 2007).

While the "mechanistic principle" identifies the common traits of phenomena which are a part of any aging process on a microlevel, the corresponding characteristic features on a macrolevel are dysfunction (which is also applied to the molecular level)

and degeneration. This can be illustrated by another definition of aging by Kirkwood: "Aging is commonly characterized as a progressive, generalized impairment of function, resulting in an increasing vulnerability to environmental challenge and a growing risk of disease and death" (Kirkwood 2005, p. 438). Another biogerontological definition of aging is given by Steven Austad: "Aging is the gradual and progressive loss of function over time … It leads to decreased health and well-being, and an increasing incidence of death, disability, … as well as disease" (Austad 2002, p. 64).

These definitions of aging as dysfunction and degeneration with death as an endpoint are connected to the next aspect of the basic definition and description of the common traits of physical aging in biogerontology. They are not merely descriptive but contain evaluative concepts already pointing in the direction of the practical goal to intervene in the aging process. Kirkwood uses evaluative concepts such as "impairment," "vulnerability," and "risk." Austad's examples are "loss" and "decreased health and well-being." From these or comparable evaluative concepts, it is only a small step to more dramatic ethical judgments. David Gems considers aging probably the worst experience that most of us will ever have (Gems 2003). In the same line, Michael Rose remarks that aging is a "many-headed monster" and a "cornucopia of suffering" (Rose 2009).

Thus, molecular damage is connected with general dysfunction and degeneration, which then leads to the experience of suffering and finally to death. For some commentators such as the political philosopher and bioethicist Colin Farrelly, this characterization of aging and consequently the gain achievable by successful interventions in the aging process can justify a "moral imperative to retard aging" (Farrelly 2008). Farrelly thus provides ethical support for a research agenda put forward by prominent experts in the field of biological aging research, among others Robert N. Butler (who also founded one of the first geriatric wards in the US and coined the term "ageism," an important concept in social gerontology), Richard Miller, Bruce Carnes, Linda Partridge, Thomas Kirkwood, and S. Jay Olshansky (Olshansky et al. 2006; Butler et al. 2008). These authors claim that slowing down aging by 7 years would be an achievable goal in the next decades. Consequently, health would be improved over the life course, presumably resulting in a compression of morbidity and a reduced risk of suffering from diseases such as cancer, diabetes, cardiovascular diseases, and neurodegenerative diseases, such as Alzheimer's disease, and others. While the medical model to treat each disease separately allegedly has failed to achieve these goals, intervening in aging processes in order to retard them is suggested as a "new model for health promotion and disease prevention for the 21st century." For this purpose, the authors, who coined the term "longevity dividend," ask for a major investment in aging research, from which this "dividend" in the form of improved health, and consequently many different economic and social benefits, could be reaped in the future.

Therefore, the concept of a "longevity dividend" perfectly illustrates how basic concepts of biological aging, practical goals, and ethical evaluations are interconnected in a biogerontological research agenda. While some biogerontologists such as Michael Rose believe that there is no separate "ethics of anti-aging," as such, an enterprise simply continues what medicine tries to achieve according to a general

social consensus (Rose 2009), this agenda and the underlying assumptions still face some important criticism. Some social gerontologists see better alternatives to developing medical interventions into aging and believe that such efforts are misguided. Such positions express the basic "conflict of interpretations" between biogerontology and social gerontology, and to understand this conflict and the rejection of the biogerontological research agenda, it is necessary to provide in the following section a brief summary of the interpretation of aging by some social gerontologists including the corresponding practical goal.

6.3 Social Gerontology: Fighting Ageism

Social gerontology is the sociological study of aging across the life course and of older age groups in society, for instance, as defined by legal provisions such as pension schemes. As in other sociological fields, both qualitative and quantitative empirical research may be carried out. This leads to a sociological description of the situation, roles, status, attitudes, and other aspects related to aging across the life course and to groups of older people. This research is focused on the challenges created by population aging, which is now a global phenomenon. Across the globe, themes like healthy aging and health, aging workforce and pensions, and intergenerational relations are of particular interest (McDaniel and Zimmer 2013).

Beyond such mainly descriptive research (and possibly the goal to support political action meeting the challenges of population aging), social gerontology has a genuine practical goal. This is the fight against ageism and age discrimination, which is complemented by the effort to develop positive models of aging (Dannefer and Settersten 2010). The concept of ageism was coined by Robert Butler in analogy to racism and sexism (Butler 1968). Butler created a basic normative orientation for the field as well as a research agenda which is closely connected to an emancipatory agenda for older people. Such an agenda would discover and systematically criticize negative attitudes towards older age groups in society and how these lead to social exclusion and the reduction of opportunities (Vincent 2009, p. 198). Butler, who also helped to frame the idea of a "longevity dividend," is an important example that beyond a mere conflict, concepts from biogerontology and social gerontology may be used in a common agenda for the future of old age. Robert Butler, who died in 2010, was the founding director of the National Institute on Aging, the founding director of the first geriatric ward at Mount Sinai Hospital, and the president of the International Longevity Center (NIA 2010). He has published a book on the "longevity revolution" outlining a possible common agenda for the different gerontological disciplines, in which he stresses that, against ageist assumptions, the increase in longevity is a major achievement of our civilization. This achievement has to be further secured and extended by improving the health of older people, also with interventions based on new biogerontological knowledge (Butler 2008).

Leaving this more general agenda aside for the moment, it can be stated that, for many social gerontologists, the primary objective of their own discipline is the fight against ageism. According to John Vincent and Dale Dannefer, this agenda can be described as a general aim of social gerontology, which defines the very core of the discipline. However, it may still be more important and characteristic for a particular theoretical current: the group of critical theories of social gerontology. In a review of this particular theoretical approach, Carroll Estes sees the theoretical fundament of these theories in the proposition that old age and the problems of older people are socially constructed. In this sense, both phenomena are the result of social interpretations of aging and old age underlying the respective constructions. Consequently, for Estes, the common trait of these theories is a form of criticism of ideology, which examines and attacks the preconditions and underlying cultural conceptions of social structures (Estes 2001).

Vern Bengtson and his coauthors categorize this critical and constructivist perspective among the third generation of theories in social gerontology. They assume that since the 1950s there is a generational overturn in theory every decade. To determine the theoretical foundations of different approaches and their influence Bengtson et al. (1997) examined the explicit theoretical framework of 645 articles which have appeared in eight of the main journals in the sociology of aging. Among those articles only 18 % referred to a theoretical foundation; however, the majority claimed to lean on a social constructivist or critical approach. Evidently this is still a minority if one considers social gerontology as a whole. But among those authors who build on more elaborated theories, this overall minority may represent a strong influence (Bengtson et al. 1997).

In a newer article, Bengtson and colleagues find that although other theories have gained a stronger influence, there are still a substantial number of authors referring to critical or constructivist frameworks (Alley et al. 2010). Beyond this, many different approaches also refer to such theories including feminist, hermeneutical, Marxist, and postmodern positions. This shows that there is a high diversity and richness of theoretical conceptions and their application. For the purpose of this chapter, it should suffice to focus on one particular aspect of those theories—how they commonly understand the concept of meaning. Bengtson notes that the underlying conception is as follows: "social meanings of age and self-conceptions of age arise through negotiations and discourse" (Bengtson et al. 1997, p. 74). Of particular interest is the term "hermeneutical," which occurs in the list of different theoretical positions above. Bengtson's remark on how social meanings arise gives an indication that in some sense all critical and constructivist theories in social gerontology are hermeneutical.

Hermeneutics is the theory of interpretation of all kinds of expression. This can be linked with a critique of the ideology which produces such expressions as Jürgen Habermas required (Habermas 1971, orig. Habermas 1968). For Paul Ricœur, a hermeneutical discipline is a set of rules for such a critique and interpretation of meaning including the systematic justification of such rules. If different layers of meaning are laid open and analyzed from a critical perspective, Ricœur also refers

to a "hermeneutics of suspicion." Friedrich Nietzsche's genealogy of morals is an example. He interprets the meaning of different conceptions of morality such as compassion based on the assumption that they are the expression of historical conflicts of power (Ricœur 1974).

In the same sense, critical social gerontology can be understood as a hermeneutical discipline of suspicion. What critical social gerontologists suspect is that certain social meanings and practices of old age, in particular if they are based on negative images of old age, are expressions of ageism. This leads to the "conflict of interpretations" between biogerontology and social gerontology.

6.4 Unsuccessful Aging Versus an Ageist Culture in the Natural Sciences

By the term "conflict of interpretations," the French philosopher Paul Ricœur means the disagreement of certain hermeneutical disciplines as to the meaning of a certain category of linguistic or nonlinguistic expressions, for instance, religious symbols and texts. While for some, religious expressions point to a positive experience of the sacred, for others they merely express social or psychological function. The corresponding layers of meaning can be discovered using hermeneutical techniques and rules of critical interpretation (Ricœur 1974).

In the present context, the analogy to Ricœur's conflict of interpretations can be drawn only to a certain degree. Obviously, there is no "conflict of interpretations" between biogerontology and social gerontology in the sense that both are hermeneutical disciplines. While in social gerontology some hermeneutical approaches exist, biogerontology as a natural science has a completely different methodology. However, there is one interpretative aspect in biogerontological research. The basic definitions of aging as an increase in physiological dysfunction and an accumulation of molecular damage are guiding the identification and categorization of phenomena as being a part of physical aging. This implies a presupposed basic understanding of physical aging on the macrolevel including its main characteristic features. Consequently, this basic understanding attributes a certain meaning to aging which also provides a fundamental orientation on a molecular, physiological level. The general rule that aging is a certain type of dysfunction leads to an identification of a certain molecular phenomenon as being a part of aging. As this general rule of identification easily leads to a particular evaluation, it also underlies the practical goal of biogerontology to intervene in the aging process in order to prevent it and, consequently, age-associated diseases.

The conflict between biogerontology and social gerontology that ignites from this basic characterization is essentially about the answer to one question: To what extent is a negative evaluation of aging justifiable? Consequently, this is not only a conflict about the theoretical meaning of different conceptions of aging but rather a conflict about the appropriate practical goals in aging research.

This particular nature of the conflict becomes visible in two statements of prominent figures in each field, Steven Austad from biogerontology and John Vincent from social gerontology. For Steven Austad, "successful aging"—one of the key concepts in psychological and social gerontology to indicate a positive sense of the experience of aging—is a contradiction in itself. Aging successfully is really impossible if one faces the biological reality of aging processes. This is captured in the sentence that "virtually everything which can go wrong, goes wrong" (Austad 2002). On the other hand, John Vincent, who positions himself among the group of critical social gerontologists, sees biogerontological concepts determined by an ageist culture (Vincent 2008).

Vincent formulates the alternative visions of biogerontology and social gerontology, including the resulting conflict, very clearly. The most important question of gerontology from his perspective is the evaluation of aging: "The key issue for gerontology is not are you for or against science, but rather are you for or against ageing. Are you for a cultural revaluation of ageing or do you want to abolish it?" (Vincent 2008, p. 333). Vincent denies that this is an antiscience stance, but for him the goal to prevent aging processes is in itself an expression of ageism (Vincent 2003, p. 683). His critique of biogerontology is of particular interest in the present context, because he applies the hermeneutical method of critical social gerontology to unmask the layers of meaning in biogerontology resulting from the alleged underlying culture of ageism on which, according to him, biogerontology is based.

The fundament of John Vincent's critique is that biogerontology integrates negative stereotypes of aging and old age already in its fundamental, presupposed general definition of aging. This is basically repeating the above statement that the general definition of biological aging guides the identification of phenomena as part of the aging process. Vincent sees this as a circular and one-sided approach, which only discovers what has already been presupposed, and excludes anything that would contradict the presupposed definition. This leads necessarily to confirmation and reinforcement of the ageist culture from which the original concepts are derived.

Since 2002, John Vincent's research is focused on these aspects of biogerontology and anti-aging medicine. By means of interviews, observations from scientific conferences, and analyses of different texts of biogerontology, he reconstructs and criticizes the alleged underlying account of aging. His special perspective is owed to the underlying ethical concern to refute negative accounts of aging in society. This corresponds to the general emancipatory approach in gerontology. Out of this motivation, Vincent attempts to prove empirically that biogerontologists are misguided in their underlying fundamentally negative accounts and prejudiced in developing their conception of biological aging. These would come down to social constructs which would give rise to misconceiving and mistreating aging. Vincent aims at substituting these negative interpretations with his own more positive ones, which he claims to be superior scientifically and ethically.

Vincent's approach exemplifies the conflict of interpretations between biogerontological and social-gerontological interpretations as cited above. He fervently wages the struggle against discrimination on the grounds of age as a fundamental normative

concern of social gerontology. Vincent thus connects his critique of biogerontology with the practical goal of social gerontology and ethical judgments. Hence, his position must be of utmost importance in attempting an ethical evaluation of the practical goals which gerontological research should try to achieve. Necessarily, such an analysis centers on the question of whether interventions into the process of aging may be desirable from the perspective of the individual. While Vincent's critique may be representational of the antagonism between the two disciplines of gerontology, he still remains a supporter of a specific branch of social gerontology, "critical" social gerontology.

At first glance, Vincent's criticism seems to be well justified. Biogerontology presupposes an implicitly negative account of aging, which is never subject to proper reflection, and the production of biogerontological knowledge is guided by the principles of this account. However, Vincent's own position lacks a fundamental ethical justification as well and he neither reflects whether negative evaluations of aging may be at least partially legitimate nor does he justify his own positive perspective on old age and aging. His position thus shares with biogerontology the shortcoming of an elaborated justification of its normative dimension. There are also particular problems related to his methodology, which result from basic conceptions of his theoretical background in critical social gerontology; the assumption that all definitions and scientific conceptions of aging are social constructions leads to such problems.

6.5 Resulting Problems

Both sides in the conflict of interpretations face different problems because they overlook the ethical dimension of their theoretical conceptions and related practical goals. Biogerontology has the tendency to connect a naturalistic concept of aging with a negative ethical evaluation of aging. This overall conception is then expanded to a more complex phenomenon, aging as a part of the life course and a human experience. An example is David Gems who states that aging may be the worst experience many of us will ever have. What he refers to is the accumulation of molecular damage and the increase in dysfunction possibly leading to pathology (Gems 2011). This is a good example for an ethical evaluation which has been named is-ought-fallacy by philosophers since David Hume. Dysfunction in a biological sense does not imply that the experience is bad in an evaluative sense. This does not mean that Gems could not argue that physical aging is indeed a bad experience. However, he is taking a short cut without the necessary consideration of evaluative premises in his argument. Even if aspects of molecular aging may lead to physical suffering, there may be a compensation for this on the level of subjective experience. If there is no biological purpose of aging, there still may be a purpose of the subjective experience of aging over the life course and to lead a "fully human life," as, for instance, Vincent claims (Vincent 2009). The conclusion that physical aging is bad can only be upheld if confronted with such assumptions. If in the

context of a "fully human life" the experience of physical aging would be beneficial, for instance, by providing an indispensable insight into important aspects of the human existence, it would have to be reevaluated in the light of this possibility.

While biogerontology thus may prematurely generate negative evaluations of aging from biological facts, social gerontology could too easily overlook negative aspects of aging by attributing them to ageism. Just denying the negative character of some aspects of aging could lead to an overly positive evaluation, which tends to overlook actual problems or overestimate the validity of claims that some experience has to be part of a good life for everybody. Such claims may be difficult to justify in a pluralistic society with many different conceptions of what a "good life" means.

Critical social gerontology faces the additional problem that understanding either scientific or cultural meaning as merely socially constructed could lead to an epistemological and ethical relativism. Although Vincent stresses that his critique is not intended to be antiscience, it can be read in a way that questions the validity of scientific methods in a general sense if these are either not appropriate to understand what basically is the result of a social construction or if using these methods produces in turn nothing but social constructions. This may as well be extended to subjective experiences of aging. If these are negative, one could equally argue that such negative experiences are only the result of social constructions, which could then imply that these experiences cannot claim any objective or intersubjective validity.

The overall problem created by the conflict of interpretations can be summarized as follows. Instead of developing a complementary theoretical and practical approach on aging, both scientific disciplines put forward contradictory views. This may not just hinder cooperation between the fields but also hinder advancing the understanding of aging and an appropriate research agenda based on the knowledge acquired in each discipline. An interdisciplinary dialogue should be the focus of a common effort to avoid such shortcomings. Such a dialogue would have to address the mutual criticism including the possible methodological limits of each perspective, different conceptions of aging insofar as they inform the practical goals of each discipline, and the underlying ethical premises. Three steps can be suggested for such a dialogue. Firstly, a starting point would be for researchers both from the bio- and the social-gerontological current to acknowledge the limits of their perspective. Secondly, it would be important to discuss the negative aspects of aging, as they are at the center of the disagreement. Finally, a future interdisciplinary outlook would be based on identifying common themes in the understanding of aging. These three steps shall be briefly sketched in the following outlook.

6.6 An Interdisciplinary Dialogue as a Possible Way Out

It is obvious that each of the gerontological disciplines has its limits and should accept its limited perspective on aging. Therefore, a more comprehensive approach is needed in which the different perspectives complement each other. The same applies to the practical goals which are both worthwhile pursuing and may even

depend on each other, as healthy aging may not be possible without a successful reduction of ageist stereotypes and vice versa. Overall the conflict of interpretations and the resulting problems makes the interdisciplinary cooperation of biogerontology and social gerontology difficult, which is necessary to bridge the theoretical and practical gaps. The problems can only be solved if, on the one hand, the validity of scientific knowledge is accepted and while recognizing its limits. On the other hand, the limits of a critical perspective and its implications also have to be addressed.

The limits of the natural sciences may be obvious from an external perspective but are nevertheless hard to accept for some scientists who want to expand their explanatory model to all kinds of phenomena. The first problem with this expansion is the diversity of aging considered as a cultural and psychological phenomenon. Reducing the general meaning of aging to physical aging oversimplifies this diversity. The second problem is the is-ought-fallacy which has been described above. The evaluative premises underlying the practical goals of biogerontology need a normative and ethical justification. There is no self-evident step from the descriptive term "dysfunctional" to an evaluation of being "bad." This does not imply that such a justification is not possible, or even that it is very difficult. However, the ethical premises of any practical goals have to be spelled out clearly so that an ethical reflection can consider them in a more comprehensive context of ethical arguments. An ethical premise which is based on the assumption that aging leads to suffering would have to be considered from different conceptions of happiness and self-determination with the perspective of the life course and the human life considered in its biographical dimension.

The main problem for a critical social-gerontological approach—as important as it is—is the conception of aging as a social construction that is used by the natural sciences or other groups in society. In a basic sense also this conception is evident as the meaning of aging is created by social practices, language conventions, legal provisions, etc. However, taken to an extreme—as some social gerontologists such as John Vincent apparently do—this concept implies that aging and its experience are nothing but social constructions, including all problems that older people face in society. Despite the emancipatory intentions which presuppose a practical goal which is objectively worthwhile to pursue, a radical constructivist perspective necessarily leads to a theoretical and practical relativism. Basically, the argument is a skeptical one, insofar as the validity claims of scientific knowledge are rejected because this knowledge and its practical application are based on unproven premises and guided by one-sided perspectives. But as any other forms of skepticism, this one also faces the problem that its arguments may be turned against itself, which undermines the validity of the criticism it formulates. Its own conceptions then become just another form of social construction, and its practical goals just guided by vested interests. The relativistic consequence would be that biogerontological or social-gerontological perspectives become two alternatives from which one may arbitrarily chose, however, without any side having the better argumentative basis.

Both methodological and ethical reflections are needed to avoid this relativism. The methodological reflection has to determine the limitations of the concept of a "social construction" of phenomena. The philosopher John R. Searle has developed a

theory of social construction of linguistic meaning, social functions, and institutions, which could also provide a model in the present context. Searle's basic condition for his own conception of social construction is that the validity of scientific knowledge is accepted. For Searle this knowledge describes "basic facts" of the structure of the universe. He gives two examples for theories of such basic facts: particle theory in physics and evolutionary theory in biology (Searle 2010, p. 4). Searle also confirms that there are problematic consequences if such basic facts are not accepted. This does not only lead to relativism but also to problematic metaphysical positions such as dualism or trialism (Searle 2010, p. 4).

John Searle does not defend a form of reductionism, which wants to explain linguistic, mental, or social phenomena on the basis of natural science. A detailed description of this theory is beyond the scope of this chapter, but a brief sketch of some of Searle's basic ideas may illustrate how it could be useful in the present context. The key concept is intentionality which helps to understand how meaning is created and relates to the world. Intentionality can also be collective, for instance, in so-called social status declarations. Such declarations provide a legal status to certain phenomena. This is also applicable to aging and groups of older people and should be the starting point of any conception of social construction, which wants to examine creation of meaning in a critical perspective. Evaluative attitudes belong to the so-called background of a society which can be analyzed from a critical perspective. But this critical perspective has to respect "basic facts" of scientific knowledge and the validity claims connected to collective intentionality. This does not mean that both cannot be criticized. But a better methodological foundation and a better ethical justification for such criticism have to be provided.

This leads to the second step in a way out of the conflict of interpretations. A key problem in this conflict is the negativity which is attributed to aging. Biogerontologists draw the practical conclusion that aging has to be prevented from the premises that it is a degenerative process and that this process causes age-associated diseases. But do these premises also imply that aging—at least physical aging—is bad for an aging person? For some biogerontologists it seems so. This leads to the criticism that biogerontology moves in a circle, from ageist preconceptions to the conclusion that aging is bad, and a confirmation of negative aging stereotypes in society (for an extensive discussion of these problems in German language, see Ehni 2014).

The problem here is that any negative evaluation of aspects of aging might be considered as an expression of ageism. Also some social gerontologists warn that an overly optimistic account of aging might lead to positive stereotypes which in turn have their problematic consequences, for instance, ignorance of health and other problems of the oldest old (Commission for the Sixth German Government Report on the Elderly 2010). The gerontologist Harold Moody refers to such positions as "gerontological correctness" (Moody 2001). Additionally, any attempt for a reevaluation of negative aspects under consideration of a bigger context in which they allegedly lead to a positive value has to be examined carefully.

Such attempts may follow the problematic pattern of a justification of individual harm or other negative experiences in respect of a greater social good or in a historical or religious teleology. This has been described as a general tendency of a positivation

of different forms of evil (cf. Ehni 2012). In contrast to this, negativity has to be taken seriously on an individual level, and any positive sense which someone may ascribe to it including considerations of overall happiness or a fully human life has to be evaluated very carefully from the perspective of individuals and of a corresponding consideration of ethical theory. In general, a strong case for the negativity of aging can indeed be made from its connection to disease and consequently to suffering. Dysfunction may lead to a reduction of capabilities and agency in general, which contribute to reduced opportunities and individual freedom. But a discussion on how this should be evaluated from an individual perspective, how important it actually is for persons to face such reductions in agency while they age, and what options there are to deal with this type of experience should benefit from the philosophical tradition of a theory of the good life, which recently was renewed by philosophers such as Martha Nussbaum (Nussbaum 1992).

Finally, in a third step after examining methodological limitations and possible ethical justifications, an interdisciplinary dialogue can search for a common ground in the mutual understanding of aging in biogerontology and social gerontology. Conceptions such as "diversity" and "plasticity" of aging which are put forward and defended by experts from both disciplines may provide such a starting point. Some studies combine conceptions from both disciplines such as social determinants and biomarkers of aging research (Epel et al. 2004; Kuh 2006). "Active aging" or "healthy aging" may be goals which can be supported by both sides, if they acknowledge the limits of their own perspective. For biogerontologists, this would imply that they have to consider that aging is not merely a physiological phenomenon, and activity and health can be understood in degrees which are achievable despite of loss of physical functions. Social gerontologists on the other hand may have to accept that there may be physiological limits to activity or health which cannot be surmounted. Indeed, Robert Butler who coined the term ageism is also one of the authors of the idea of a "longevity dividend" which may result from successful interventions in the aging process. In the end, there may not be a generally valid answer to the question, to which extent aging can be active, successful, and healthy. If aging points to the finitude of the human existence, the relevant question is our evaluation of death. For some, death may provide sense and fulfillment to a human life in the same way as a curtain to a theater piece. For others, death is an outrage, a denial of the meaning of the life.

All this does of course not mean that a conflict of interpretations should be fully solved and replaced by a single view on aging. Competing perspectives are necessary and desirable. But disagreements should nonetheless be based on mutual methodological comprehension, an interdisciplinary dialogue and cooperation. Achieving a better understanding of the conflict of interpretations in aging research may contribute to mutual comprehension of the other disciplines' goals and a more productive scientific dispute.

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Part II
What Constitutes Health and Cognition in Old Age from a Life-Course Perspective?

Chapter 7
Occupational Gerontology: Work-Related Determinants of Old Age Health and Functioning

Jenni Kulmala and Mikaela B. von Bonsdorff

7.1 Occupational Gerontology

The concept *occupational gerontology* was introduced by Professor Willem Goedhard. This concept brings together two aspects: occupational health and ergonomics concentrating in research on working life and gerontology concentrating on research of aging and older people. Occupational gerontology deals with the questions concerning older workers, maintaining work ability during the life course and the longitudinal effects of work on old age outcomes. The aim in occupational gerontology is to provide better understanding of the questions related to older employees while also investigating how work influences aging in terms of health and well-being after retirement. In the spirit of active aging, occupational gerontology investigates also topics related to bridge employment and volunteering during retirement. The aim is to increase understanding about the association between occupational factors and aging processes (Goedhard 2011).

7.2 Work Ability

Work ability is a multidimensional concept that has changed over time. When using a medical-based approach, work ability can be described as a balance model which is based on the stress–strain model by Rutenfranz (1981). In the balance model,

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work ability can be defined as equilibrium between employees' perception of the demands of the work and his or her ability and resources to cope with those demands (Ilmarinen 2006). Work ability can be described by a multidimensional model and depicted as a house that consists of four floors and the surrounding immediate environment (Ilmarinen et al. 2008). The first three floors include individual resources such as health, functional capacity, knowledge, skills, motivation, and values. The fourth floor includes characteristics of the work such as work conditions, content and demands of the work, organization, and community and work tasks. The immediate structures that surround the individual support work ability and these include the community and family. Work ability is a dynamic construct with changes that occur on an individual level and in the work context. For example, aging influences work ability through changes that occur in health and functional capacity. Work ability decreases with increasing age. It is also known that older male employees typically have better work ability than women of the same age partly due to the overall higher physiological reserve in men than women (such as muscle strength and oxygen consumption) (Gould et al. 2008). Work ability differs also according to occupation, and those who are working in managerial positions report better work ability than blue-collar workers (Gould 2008).

The Finnish Institute of Occupational Health developed the Work Ability Index (WAI) in the 1980s for measuring work ability (Ilmarinen et al. 1997; Tuomi et al. 1998). WAI was originally developed to serve as a tool when evaluating the work capacity of the individuals in a clinical setting. Since then, it has also been used as a research instrument and it has been validated against clinical data (Eskelinen et al. 1991). It is a widely used measure available in 20 languages (van den Berg et al. 2008). WAI consists of seven items concerning subjective assessments of current and anticipated future work ability, sickness absences, the number of physician-diagnosed illnesses, and psychological resources. The first item of WAI is about current perceived work ability compared to the lifetime best, and it has been used as a single measure to assessed perceived work ability (Tuomi et al. 1991).

Several factors influence work ability which is a multidimensional and dynamic construct. In a study using data from the Health 2000 Study in Finland, the prevalence of chronic illnesses such as cardiovascular disease, diabetes, musculoskeletal disorders, mental problems, as well as decreased physical, cognitive, and social functioning was related to decreased work ability in the working population (Koskinen et al. 2008; Sainio et al. 2008). Mental and physical work strain has also been found to be related to decreased work ability (Lindberg et al. 2006; van den Berg et al. 2008).

7.3 Job Strain and Stress

In the following section, commonly used definitions of work-related mental and physical strain and stress are described. Further, the adverse health effects caused by different kinds of job strain and stress are discussed.

7.3.1 Mental and Physical Job Strain

Job strain can be described as the discrepancy between the demands of the work and the level of control that the individual has over the work. The most widely used measure for assessing perceived mental job strain is the Job Demand-Control (JDC) model put forward by Robert Karasek (Karasek and Theorell 1990; Karasek 1979). The original measure included the dimensions of psychological job demands and job control or decision latitude which is assessed with two subscales of skill discretion and decision authority. The JDC model was later expanded to include social support as a third dimension indicating iso-strain. Job control comprises the two subscales of skill discretion also referred to as task variety and decision authority which has been referred to as autonomy or social authority over making decisions. These two subscales together form the scale of job control. The two dimensions, job demand and job control, together form four job strain combinations of high job strain (high demands and low control), active job (high demands and control), low job strain (low demands and high control), and passive job (low demands and control). The two dimensions of job demand and control can also be used separately. The "effort–reward imbalance" is a complementary model developed by Johannes Siegrist (1996). In the model, a discrepancy between the efforts the employee invests in work and the rewards he/she received from the employer is considered to cause psychobiological stress and predict negative health outcomes in the long run. The rewards that the employees receive include financial rewards, career opportunities, and job security.

Perceived physical job strain has been commonly assessed by inquiring about work-related cardiorespiratory and musculoskeletal strain. Although machines are commonly taking over or helping with the manual tasks in work, there are still a lot of work tasks that need to be done by humans that cause physical strain to the body.

7.3.2 Work-Related Stress

Mental job strain and perceived work-related stress correlate closely. However, there is no clear consensus in the previous literature about the definitions of stress. The term stress is sometimes used when describing slightly challenging situations, or on the other end, it may mean a severe medical condition, which can lead to physical symptoms and inability to work.

In the biological perspective, stress is a physiological reaction to psychological stress, involving the hypothalamic–pituitary–adrenocortical and sympatho-adrenomedullary axes (Koolhaas et al. 2011). Dr. Hans Selye is considered as one of the founding fathers of the concept of stress. According to his thinking in 1956, stress is the "non-specific response of the body to any demand for change." A little later, more psychological definition was created by psychologist Richard Lazarus, who described stress as "a psychological reaction, where a person feels that he

cannot adequately cope with the demands being made on him" (Lazarus 1966). A recent review article discussed the term stress and its use in current literature. This review provides a critical evaluation of the stress concept and in conclusion suggested that the term stress should be "restricted to conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability" (Koolhaas et al. 2011).

Work-related stress is defined as a "pattern of physiological, emotional, cognitive and behavioral reactions to some extremely taxing aspects of work content, work organization and work environment" (Houtman et al. 2007). Work-related stress reactions often manifest as mental exhaustion, depression, anxiety, memory problems, somatic symptoms, and sleep-related disturbances, and these symptoms can be occasional or they may also be present for several years (Kulmala et al. 2013; Nakao 2010; Potter et al. 2009). The terms burnout and work-related stress are often used as synonyms. However, burnout is a medical condition, which is caused by prolonged exposure to work-related stressors. It commonly refers to more serious condition including three main dimensions: emotional exhaustion, depersonalization, and reduced performance ability and motivation (Kaschka et al. 2011).

High job demands, low job control, low coworker support, low supervisor support, low relational justice, and a high effort–reward imbalance are strong risk factors for stress-related disorders (Nieuwenhuijsen et al. 2010). Further, emotional demands and job insecurity increase the risk for stress-related disorders (Nieuwenhuijsen et al. 2010). Also roles in the organization, supervisory relationships at work and the organizational structure, as well as job satisfaction play a significant role in stress development (Fiabane et al. 2012; Finney et al. 2013).

Work-related stress is a well-acknowledged problem. There is, however, no clear consensus about its prevalence. The rates vary between study populations and occupations (Quattrin et al. 2010; Ruitenburg et al. 2012). Several operationalizations of perceived stress have been used. Nevertheless, it has been estimated that in Europe nearly 30 % of adult workers suffer from stress which is related to work (Houdmont et al. 2010).

7.3.3 The Adverse Health Effects of Work Strain and Stress

Mental job strain or its components, i.e., high job demand or low job control, correlate with an increased prevalence of several chronic illnesses and mortality in cohort studies around the world. The contribution of high job strain to cardiovascular disease has been studied widely. A recent meta-analyses by the IPD-Work Consortium (Kivimäki et al. 2012) investigated the effect of job strain on coronary heart disease in almost 200,000 working individuals and concluded that the risk was higher for those who had higher job strain. High job strain has also been linked to other important chronic illnesses and conditions such as diabetes and obesity. Using data from the Whitehall II study, Heraclides et al. (2009) found that high job strain doubled the risk for diabetes among healthy civil servants in a 15-year follow-up.

A Swedish study linked low job control professions with an increased prevalence of stroke in a register-based study including nearly three million working individuals (Toivanen 2008). High mental job strain has been shown to be related to an increased risk of premature all-cause and cause-specific mortality, albeit some studies have reported nonsignificant associations. Eaker et al. (2004) found that high job strain was not related to mortality or coronary heart disease in a 10-year follow-up among men and women in the Framingham Offspring Study. Since job strain is associated with higher smoking prevalence, physical inactivity, and higher use of alcohol (Heikkilä et al. 2013; Nyberg et al. 2013), lifestyle factors may explain at least part of the association between job strain and chronic diseases.

Although physical activity is known to protect from several adverse health effects, a few studies have reported that certain kind of physically demanding work may also have detrimental effects on health. A study by Petersen et al. (2012) reported that among men, heavy lifting is associated with increased risk for ischemic heart disease. Especially those men with low occupational physical activity but with work that included heavy lifting had a substantially increased risk. However, it should be noted that those with occupational heavy lifting were also more likely to have a low educational level, low leisure time physical activity level, and heavy smoking, indicating that there may be also some other factors increasing their disease risk (Petersen et al. 2012).

It is well acknowledged that work-related mental stress correlates strongly with poor self-rated and objectively measured health. Exposure to high-demand and low-control environment at work is associated with poor self-rated health (Silva and Barreto 2012). In addition, persons who report high effort–reward imbalance and overcommitment also report poor self-rated health (Silva and Barreto 2012). Low self-rated health is also associated with ongoing conflicts at work (Oxenstierna et al. 2011). Furthermore, a study by Toivanen (2011) reported that work stress and also poorer socioeconomic position are associated with poorer self-rated health, psychological distress, and musculoskeletal pain. Their study also showed that the joint health-decreasing influence of work stress and low socioeconomic position is additive.

Psychosocial stress at work is also a relevant risk factor for depressive symptoms and other mental problems (Chen et al. 2009). A cross-sectional survey, conducted among 561 Chinese offshore oil workers by Chen et al. (2009), showed that especially conflicts between job and family/social life, poor development of career and achievement at work, safety problems at work, management problems and poor relationship with others at work, poor physical environment of the work place, uncomfortable ergonomic factors at work, and poor organizational structure at work were strongly associated with poorer mental health (Chen et al. 2009). Also a meta-analyses by Bonde (2008) including company or population-based follow-up studies with some 63,000 employees provided consistent findings that adverse psychosocial factors in the workplace elevate the risk of subsequent depressive symptoms or even major depressive episodes (Bonde 2008). Work-related stress correlates also with poorer self-esteem, and it has been suggested that poor self-esteem may contribute to the relationship between work-related stress and depression (Lee et al. 2013).

The association between mental stress at work and old age dementia has been acknowledged. A study by Wang et al. (2012) investigated a cohort of 913 community dwellers, aged 75 years and older, from the Kungsholmen Project and showed that lifelong work-related psychosocial stress is strongly associated with increased risk of dementia and Alzheimer's disease in late life, independent of other known risk factors (Wang et al. 2012). Similar findings have been reported about the association between work-related stress and increased risk of vascular dementia in the population-based Study of Dementia in Swedish Twins (Andel et al. 2012). However, most of the previous studies have comprised relatively short follow-up periods, and there is still relatively little information available about the long-term consequences of stress.

Along with job strain and stress, poor work ability also predicts adverse health events. It has been shown that poor work ability correlates with earlier retirement (Alavinia et al. 2009). In a representative group of middle-aged Danish workers, people with reduced work ability had an increased risk of long-term sickness absence and early retirement (Sell et al. 2009). Also periods away from work, especially due to unemployment or sickness, are shown to be associated with adverse old age outcomes, such as lower cognitive status (Leist et al. 2013).

7.4 Positive Effects of Work on Health and Functioning

Although unfavorable working conditions may lead to poorer health and functioning, work may also have several positive influences on well-being. Work may provide social, psychological, and also physical benefits. In several studies, work-related factors have been linked to better mental and physical health. Work may have positive effects on social relationships and thus promote health and well-being through social support provided by the network of colleagues (Silva and Barreto 2012; Suzuki et al. 2009).

In addition to social networks, work-related physical activity has been one of the main interests in occupational gerontology for several decades. As early as the 1950s, one of the public health pioneers, Jeremy Morris, provided evidence that physically active conductors on London's double-decker buses had lower rates of coronary heart disease than sedentary bus drivers (Morris et al. 1953a, b). After these studies, occupational physical activity has gained growing attention. It has been reported that high occupational physical activity reduces risk of having chronic diseases, such as heart disease and diabetes independent of leisure time physical activity status (Probert et al. 2008). More occupationally physically active people have lower body mass index, lower waist circumference, and better insulin resistance (Larsson et al. 2012). Among persons who are sedentary outside of work, a high-activity occupation may reduce the risk for abdominal obesity (Steeves et al. 2012). A meta-analysis of observational studies by Wendel-Vos et al. (2004) showed that a high level of occupational physical activity protects against ischemic stroke compared with moderate and inactive occupational levels. Interestingly, in studies

conducted in the United States, the protective effect of physical activity was lower than in European studies. The authors hypothesize that may be due to generally lower level of physical activity in the US compared to Europe. Based on this meta-analyses, the authors suggested that since coronary heart disease and stroke are the first and the second most common causes of death worldwide and since these diseases are expensive to the healthcare system, increasing work-related physical activity might prevent these diseases and their adverse effects (Wendel-Vos et al. 2004).

Occupational physical activity may even reduce cancer risk. Several epidemiological studies provided evidence that there may be a decrease in breast cancer risk associated with occupational physical activity both in premenopausal and postmenopausal women (Gammon et al. 1998). It has also been reported that adult men who are continually active at work may have a decreased risk of prostate cancer (Krishnadasan et al. 2008) and similar results have reported for colon cancer as well (Parent et al. 2011). Although the biological mechanisms by which physical activity may influence cancer risk are unknown, the found associations are suggested being influenced by changes such as reduced body size and alterations in immune function and serum hormone levels (Gammon et al. 1998; Krishnadasan et al. 2008).

Further, the association between work-related physical activity and lower mortality risk has been reported in many studies (Graff-Iversen et al. 2007; Salonen et al. 1988). The study by Salonen et al. (1988) reported that the lack of leisure time physical activity and a sedentary occupation were associated with an increased risk of ischemic heart disease death in a Finnish cohort of 15,088 persons aged 30–59 years who had no history of cardiovascular disease or other condition in the beginning. According to their study, persons who were sedentary in leisure time or at work had an increased risk of ischemic heart disease death also when adjusted for age, health status, family history, and body mass index. Even after additional adjustments for years of education, social network participation, cigarette consumption, serum cholesterol level, and blood pressure level, the association for low occupational physical activity and ischemic heart disease death remained unchanged (Salonen et al. 1988). However, conflicting results have also been presented (Holtermann et al. 2012).

It should be noted that so-called healthy worker effect may cause bias to these associations. The selection bias may occur when only occupationally active people are chosen to the study and also when health-related factors influence the continuity of work. Usually persons who remain occupationally active until old age are healthier and live longer than the general population. It has been estimated that the healthy worker effect reduces the association between exposure and outcome by an average of 20–30 % (Shah 2009).

7.5 Finnish Longitudinal Study on Municipal Employees

In this section, the procedure, main outcomes, and most recent findings from the Finnish Longitudinal Study on Municipal Employees (FLAME) are presented.

7.5.1 Aims and Scope of the Study

The FLAME is a collaboration with the Gerontology Research Center (GEREC); the universities of Jyväskylä and Tampere, Finland; and the Finnish Institute of Occupational Health (FIOH, see Acknowledgments). The FLAME study was initiated by the FIOH in 1981 and targeted to 7,344 individuals aged 44–58 years old at the baseline. The aim of the FLAME was to study how work, work ability, transitioning into retirement, and lifestyle predict active aging, well-being, and need of care in old age. The focus is on work and work ability as predictors of old age health, physical functioning, participation, care need, and disability. The goal is to produce unique information on the effects of work on old age well-being and to contribute to research knowledge in the field of occupational gerontology (Tuomi et al. 1997a, b, c).

The baseline cohort in 1981 consisted of 6,257 occupationally active individuals working in the public sector. Occupational group was defined as the participants' position of employment at baseline. The 133 different occupational titles were clustered into 13 occupations based on job analysis at the work places. These were further collapsed into blue-collar (e.g., installation, home care, cleaning, and assistant nurse work) and lower white-collar (e.g., office, administrative, teaching, and registered nurse work) and upper white-collar employees (e.g., administrative and teaching work) (Ilmarinen et al. 1991).

Work-related factors, health, work ability, and stress symptoms were studied using comprehensive questionnaires in 1981, 1985, 1992, 1997, and 2009. The study population was also followed up for mortality between January 1, 1981 and July 31, 2009. Mortality data were obtained from the Finnish National Population Register. During the 28-year follow-up, 38 % of the baseline respondents died. Mortality was taken in to account in the analyses as a competing risk. In 2009 information about disability and mobility, gathered by postal questionnaires, was available for about 3,000 baseline respondents (almost 90 % of survivors). The study was approved by the Ethical Committee of the Finnish Institute of Occupational Health.

The Finnish Longitudinal Study on Municipal Employees (FLAME), with 28-year follow-up data, provides a unique opportunity to assess the early work-related determinants of functional decline.

In such a research approach, it is possible to explicitly state the temporal ordering of exposures and their outcomes. These kinds of data sets are unique worldwide and therefore have possibility to provide remarkable new findings in this field.

7.5.2 Work Ability Measures

The seven item WAI was developed at the FIOH in collaboration with the specialists in the field of occupational health in the 1980s (Ilmarinen et al. 1997; Tuomi et al. 1997b). WAI was initially designed for the FLAME. WAI includes seven items.

The first item is the subjective assessment of present work ability compared to the lifetime best, with the question: "Presume that when your work ability was at its best, the score was ten. What score would you give your present work ability?" The second item is about work ability in relation to the demands posed by the work. The third item queries the number of diseases, the fourth gathers information about the estimated work impairment due to disease, and the fifth about sick leave during the past year. In the sixth item, the participants are asked to anticipate the level of their work ability in the next 2 years, and the final question is about mental resources of the participant.

7.5.3 Mental and Physical Job Strain and Exposure in Midlife

The baseline questionnaire in the year 1981 and the follow-ups in 1985, 1992, and 1997 included several questions on demands that the work posed on an individual, the level of control that the individual had over the work, and the level of work-related exposure in the physical work environment. Items included questions on demands of the work such as pressures related to work, work pace, and time schedule. The participants were asked about the level of control of work with questions such as to what extent is it possible to influence the work environment or participate in planning of the work. According to the Karasek's JDC model (1979), job strain was assessed using the job demand and job control questions. Job strain categories of low, intermediate, and high levels of demand or control were formed, and the mental job strain measure was constructed as low job strain (low demands with high or intermediate control), high job strain (high or intermediate demands and low control), and intermediate job strain (all other combinations of demands and control).

The participants were asked about how much cardiorespiratory and musculoskeletal strain the work caused them. Cardiorespiratory strain was assessed with the question: "How often does physical exertion in your work cause: (a) sweating, (b) breathlessness and (c) heart palpitation?" and musculoskeletal strain was assessed with the question "How much strain does work cause to your: (a) arms, (b) legs and (c) back?" The FLAME study included a question on physical tasks related to the work and the amount of physical labor that was included in the work.

Occupational exposures were assessed based on the extent of physical or chemical exposures in the work environment. These were inquired by asking whether the work environment included exposures such as the following: (1) cold or hot working environment or temperature changes; (2) dryness, dampness, or wetness; (3) dirtiness; (4) dust, smoke, or steam; (5) acids, alkali, solvents, or oils; (6) noise from work machines; (7) vibration; (8) inadequate lighting; and (9) draft which decreased (or had decreased if they had transitioned into retirement) their job satisfaction.

7.5.4 Stress Questionnaires in Midlife

The stress questionnaire used in the FLAME study was constructed by a panel of occupational health experts at the FIOH using the best knowledge available in the late 1970s and early 1980s when the study was launched. In the FLAME study, self-reported stress symptoms were assessed at baseline in 1981 and 4 years later in 1985 (Elo et al. 1992; Huuhtanen et al. 1997). The items in the questionnaire were as follows: stomach pain and chest pain, dizziness, depression, anxiety, inability to enjoy daily life, difficulties in falling asleep after awakenings, difficulty remembering, remembering requires effort, blackouts, lack of energy and vitality, nervousness, gloomy outlook for the future, general reluctance, urge to stay home instead of going to work, and inclination to be off work without reason. The frequencies of these symptoms were assessed with a five-point Likert-type scale. Stress items used in the FLAME study are in line with widely used scales published after the baseline of the study.

7.5.5 Findings from the FLAME Study

Distinct trajectories of work ability changes were identified from midlife to old age (von Bonsdorff et al. 2011b). In general, work ability declined with older age but several different patterns were found. Five distinctive groups of work ability were identified for men and a four for women. About half of the participants' work ability remained on a moderate level throughout the follow-up. For the other half, the decline in work ability was more dramatic over time. Particularly for women, a U-shaped trajectory was common where work ability first declined but then increased after the follow-ups in 1992 and 1997. Of note is that during this time, most of the employees transitioned into retirement. Mental and physical job strain in midlife correlated with the work ability trajectories. Men and women who at the baseline reported that their work was not mentally or physically straining also reported excellent to moderate work ability throughout the follow-up more often than those who experienced higher job strain. People whose work ability decreased dramatically during the follow-up often reported having had higher job strain in midlife.

Work ability assessed in midlife predicted disability in old age as well as premature mortality (von Bonsdorff et al. 2011a). Work ability in midlife was lower in blue-collar professions compared to white-collar professions. Particularly among men, mortality was higher for those working in a blue-collar profession. The risk for old age disability increased with lower work ability in midlife and was higher for the blue collars. For example, even after adjusting for differences in lifestyle and the main chronic diseases, the risk of either premature mortality or disability in old age was 4.5-fold for blue-collar men and almost 3.5-fold for blue-collar women

compared to the white collars with excellent work ability in midlife. In addition to incidence of disability, work ability in midlife predicted also disability severity 28 years later (von Bonsdorff et al. 2012). Accounting for differences in socioeconomic status, living habits, and chronic diseases only slightly attenuated the association.

The association between mental job strain and all-cause mortality was investigated within the main occupational groups (von Bonsdorff et al. 2012). Low job control among men increased and high job demand among women decreased the risk of mortality during the long-term follow-up. The differences in mortality were further investigated in the job strain groups which were low strain (low job demand and high job control), active job (high job demand and high job control), and passive job (low job demand and low job control). The results showed that high job strain increased the risk of mortality among middle-aged white-collar men and passive job among blue-collar men compared to men with low job strain. Compared to the white-collar women working in a low strain job, those with active jobs had a decreased risk of premature mortality. High physical job strain also increased the need for in-patient all-cause hospital care in old age. Findings were parallel but less evident for mental job strain.

The FLAME study showed how the dominant stress symptoms may vary greatly between middle-aged people (Kulmala et al. 2013). Four midlife stress profiles were identified: negative reactions to work and depressiveness, perceived decrease in cognition, sleep disturbances, and somatic symptoms. Among persons suffering from *negative reactions to work and depressiveness*, the following symptoms were common: urge to stay home instead of going to work, lack of energy and vitality, inability to enjoy daily life, inclination to be off work without reason, general reluctance, gloomy outlook for the future, and depression. Those who suffered from *perceived decrease in cognition* had difficulties remembering and blackouts and reported that remembering required effort. Persons having *sleep disturbances* reported difficulties falling asleep, several awakenings during the night, and difficulties falling asleep after awakenings. Those whose stress symptoms were mainly *somatic* had chest pain, stomachache, and dizziness. In this study, very few participants suffered from symptoms typical for all stress profiles, indicating that the manifestations of work-related stress may be completely different between the individuals. Stress symptoms in midlife were strongly associated with poorer physical functioning in old age (Kulmala et al. 2013). Persons suffering from work-related stress in midlife had significantly higher risk for old age disabilities compared to their non-stressed counterparts. The unfavorable lifestyle factors, such as physical inactivity, higher body mass index, smoking, alcohol intake, chronic conditions, and lower family's economic situation, partly explained the association. However, even after taking a number of lifestyle influences into account, the strong and independent association between midlife stress and old age disabilities persisted. Stress has several known consequences on hormone level and even on telomere length, which is considered a measure of cell senescence and deterioration of health (Epel et al. 2004; Epel 2009). Thereby, stress may contribute to excess vulnerability to old age disabilities.

7.6 Promoting Healthy and Active Aging by Occupational Gerontology

Within this chapter, we have given a brief overview how work and work-related determinants are affecting individual's health and well-being. The effects of work may be positive or negative, and they may be seen immediately or even come into sight after the decades. Since occupationally active years take about half of our lives, it seems very well grounded to pay additional attention to work when aiming to promote healthy and active aging. Mental and physical work strain and work-related stress increase the risk of adverse health events even long after retirement. Therefore, paying attention to quality of working life may have long-term beneficial effects.

So what should be done based on these findings? Interventions aiming to prevent stress, improve mental health, increase job satisfaction, and improve job effectiveness have positive effects on employees' mental health. Interventions include, for example, stress management training, including relaxations and meditation, educational workshops, and counseling (Czabala et al. 2011).

Interventions effective in preventing work-related burnout include cognitive behavioral training, psychotherapy, counseling, adaptive skill training, communication skills training, social support, and relaxation exercises. In addition, interventions directed to organizations including work process restructuring, work performance appraisals, work shift readjustments, and job evaluation seem to be generally helpful in reducing burnout and its components. The interventions combining measures directed towards individuals and organizations are shown to have more positive effects than either person- or organization-directed interventions alone (Awa et al. 2010). These kinds of intervention programs do not just increase the quality of life of working aged people, but they may also have positive effects extending into old age.

Interventions including exercises, relaxation, physical applications, biofeedback, and workplace adjustments for adults suffering from the work-related complaints of the arm, neck, or shoulders might have beneficial effects in reducing work-related physical complaints (Verhagen et al. 2007). Even adjustable chairs may reduce the severity, intensity, and frequency of musculoskeletal pain among workers who are required to sit for prolonged periods (van Niekerk et al. 2012).

The FLAME study findings support the idea that when aiming to promote healthy, active, and independent old age, work-related factors in midlife and possibly even earlier should be taken into account. Preventing work-related stress and adverse strain may lead to more healthy and independent old age, which is preferable not only for the individual but also for the society. Healthy and active older people are an asset to the society, their families, and to the third sector. Promoting health and functioning during the work career will potentially have both short-term and long-term benefits on individual and society level.

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Chapter 8
Social, Behavioral, and Contextual Influences on Cognitive Function and Decline over the Life Course

Anja K. Leist and Johan P. Mackenbach

8.1 Introduction

Maintaining cognitive function is a prerequisite for living autonomously in older age and it is highly desirable to postpone cognitive decline for as long as possible. In order to identify influences on cognitive function and to understand how it is shaped across the life course, it is necessary to focus on life course influences on cognitive aging that ultimately lead to clinically significant states of cognitive impairment and dementia (Singh-Manoux and Kivimäki 2010). This chapter focuses on the following research question: What social, behavioral, and environmental factors influence later-life cognitive function? The aim is to give a selective review of current knowledge with a particular focus on the most recent developments in research on cognitive reserve between 2008 and 2013.

The chapter is structured as follows: after introducing the theoretical framework of cognitive reserve, life course epidemiology, and some methodological issues, an overview on social, behavioral, and contextual factors that have been shown to shape later cognitive function will be given. The chapter ends with a short summary and prospects for further research.

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8.1.1 The Concept of Cognitive Reserve

The onset of cognitive decline is already evident in middle age (Singh-Manoux et al. 2012) and long-term cognitive decline happens before the diagnosis of Alzheimer's disease (Wilson et al. 2012a). The absolute rate of cognitive change is similar among individuals with both high and low initial scores in cognitive ability and rate of change does not depend on initial level of cognitive ability (Salthouse 2012). Despite similar levels of pathology, some individuals show clinical symptoms of disease, while others do not (Stern 2002). In order to explain this disjunction between brain pathology and cognitive functioning, the concepts of brain reserve and cognitive reserve have been introduced. Brain reserve describes individual quantitative—passive—differences in the brain, e.g., size, number of neurons or synapses, which account for differences in how individuals cope with brain pathology (Stern 2009). Cognitive reserve is the brain's ability to cope actively with pathological damage by efficiently engaging brain networks or implementing alternative strategies to solve cognitive demands (Stern 2002). Cognitive reserve is a hypothetical structure and can only be measured by proxies, e.g., educational and occupational attainment or reading ability. Higher cognitive reserve acquired, for example, by education compensates cognitive decline caused by brain pathology to some extent (Bennett et al. 2003; Stern 2009).

8.1.2 Life Course Epidemiology

The cognitive reserve hypothesis suggests that cognitive abilities are shaped over the life course and therefore should be studied using a life course epidemiology approach, which suggests that health and disease in older age are the result of multiple influences across the life course (Kuh et al. 2003; Richards and Deary 2005). It has been suggested that cognitive and emotional skills are intertwined across the life course by genetic influences, nurturing, schooling, work, and lifestyle, which "fuse to form skills for life supporting self-regulation, competence, and quality of life that persist into later life" (Richards and Hatch 2011, p. i32). Enrichment of environment and individual behaviors, intellectual, physical, and social activities can all modify cognitive development (Hertzog et al. 2008).

8.1.3 Methodological Issues

Owing to large, sometimes cross-national, longitudinal surveys with extensive measurements and the availability of elaborate statistical procedures to model data longitudinally while taking into account missing data and competing risks, it is now possible to acquire valid estimations of how social and environmental factors, dating back several decades, are related to later-life cognitive function (such as the Whitehall II study, e.g., Singh-Manoux et al. 2005). These data allow the development of dementia risk prediction models (see Qiu (2014) on the contribution of

lifestyle factors to dementia over the life course and Stephan (2014) on predictive accuracy and complexity of dementia risk models). Mainly observational in nature, most studies rely on retrospective life history assessments, or, in some rare cases, true lifespan data from early childhood to older age. There are potentially intertwined relationships between exposure and outcome and large sets of confounders have to be taken into account, such as parental socioeconomic status, current engagement in intellectual activities, depression, and physical activity. For instance, the association between education and cognitive function may be at least to some extent reciprocal in nature: not only have higher-educated individuals better cognitive function, but more gifted individuals may also stay longer in school, benefit further from access to higher education, and pursue work and leisure interests that are mentally stimulating and further enrich cognitive development. To solve the problem of causality, several studies have attempted natural experiments, by using contextual information such as schooling laws or retirement policies in order to compare the influences of education or retirement on an aggregate level (Glymour et al. 2008a; Mazzonna and Peracchi 2012). In retrospective designs, selective attrition due to mortality or morbidity may be a confounder that deserves particular attention and should be addressed by using weights (e.g., inverse probability weighting) or taking other appropriate measures (e.g., such as using multiple imputation analysis; Glymour et al. 2012a). Excellent overviews on methodological challenges in identifying causal influences on cognitive function and suggestions for solutions are given in Glymour et al. (2008b) and Jones et al. (2011).

8.2 Social and Behavioral Influences over the Life Course

This section gives an overview of social and behavioral factors over the life course that could influence later-life cognitive function, from factors indicating prenatal and early-infancy environment, parental socioeconomic status, to education and work environment, social mobility, and leisure activities.

8.2.1 Prenatal and Early-Infancy Environment

The contribution of prenatal developmental milieu on later-life cognitive function may act along the pathway of fetal origins of adult disease (Barker 1992) that has been supported by substantial evidence during the last decades. Factors like maternal prenatal stress and malnutrition (both prenatal and during infancy) may lead to increased vulnerability to later-life cognitive decline via biological pathways, which are beyond the scope of this review (e.g., Whalley et al. 2006). In a recent study, Raikkonen et al. (2013) show that birth weight, length, and head circumference are associated with later cognitive function, arguing that these variables are "crude proxies of prenatal developmental milieu and early living conditions that are affected by multiple factors with potential long-term neurodevelopmental consequences" (p. 7). Of these factors, maternal hypertension during pregnancy and fetal overexposure to glucocorticoids may serve as an example (Raikkonen et al. 2013).

8.2.2 Parental Socioeconomic Status

Parental socioeconomic status is usually conceptualized by paternal and maternal education and occupation, as well as material resources (availability of household items, home or car ownership). Rogers et al. (2009) found that low parental education is associated with risk of late-life dementia in the USA. Adjusted for paternal education, low maternal education was also found to be associated with higher risk of dementia or cognitive impairment.

Recent studies suggest that early socioeconomic conditions, such as parental socioeconomic position (SEP), mediate the relation between prenatal factors and later cognitive function (Zhang et al. 2009). The extent to which parental socioeconomic status acts independently on later-life cognitive function differs across studies. Some studies provide evidence that early SEP is largely mediated through adult education and later-life measures of SEP (Singh-Manoux et al. 2005; Osler et al. 2012; Richards and Sacker 2003), or chronic stress (Evans and Schamberg 2009). Another study has found an independent contribution of early-life SEP on later-life cognitive function (Fors et al. 2009). There is even evidence for protective effects of early-life adversity on cognitive decline in African-Americans (Barnes et al. 2012), with food deprivation and lower BMI than average in early life being associated with a slower rate of cognitive decline. However, it cannot be ruled out that sample composition in terms of a "selective survival" effect contributes to this finding.

A quite specific exposure that to some extent reflects parental socioeconomic position may be the number of books at parental household during childhood. In our own analyses, we investigated the impact of number of books at parental household at age ten with 6-year cognitive aging trajectories including verbal fluency, immediate and delayed recall. No association with a global indicator of cognitive function (averaged z-scores of the three tests) was found, but contrasting patterns were observed for different cognitive domains. Having fewer books at the parental household was associated with slower aging-related decline in verbal fluency, but significantly faster aging-related cognitive decline in immediate and delayed recall (Leist and Avendano 2013).

8.2.3 Education

Education is, over and above country-specific schooling laws (years of compulsory schooling, costs of schooling), parental experiences or expectations towards schooling, and others, to some extent determined by childhood cognitive ability. Early cognitive abilities are strongly associated with later cognitive function (Richards and Sacker 2003), cognitive decline (Richards et al. 2004), and risk of late-onset dementia (Whalley et al. 2000). Several studies have also found that parental occupation is linked to cognitive abilities during childhood and early adulthood (Osler et al. 2012). With an ever increasing number of studies on how early cognitive abilities shape later educational and occupational attainment, determine health behaviors, are associated with deviant behavior, etc. cognitive abilities during childhood (intelligence) have

been claimed to be the "fundamental cause" of social inequalities (Gottfredson 2004; Gottfredson and Deary 2004; Deary and Batty 2007).

It is difficult to differentiate between education and cognitive function, as both are reciprocally determined (Jones et al. 2011). Deary and Johnson (2010) discuss that education and intelligence have the same underlying genetic predispositions and are intertwined in epidemiological studies. The authors rightly point out that "It is clear that not everyone derives the same benefit from any given educational opportunity and that the same educational opportunities are not available to everyone." (p. 1367). Education, as an early-life influence, seems far more important for the development of cognitive function than later influences such as later-life SEP or socioeconomic mobility (Karp et al. 2004; Parisi et al. 2012). This is in line with claims that cognitive function is more amenable to training in earlier life stages, in the sense of a "window of opportunity" hypothesis (Kuh et al. 2003).

One of the main developments in the last decade in research on cognitive aging is knowledge about the trajectories of cognitive function. Whereas earlier longitudinal studies identified that several factors, such as education, influence the rate of cognitive decline, newer evidence suggests that rather few factors are associated with the rate of decline for individuals with both high and low initial cognitive scores, especially if potential methodological biases (such as regression to the mean) are adjusted for (Salthouse 2012). Further, consistent evidence is found for high- and low-educated individuals declining at similar rates (e.g., Glymour et al. 2012b; Early et al. 2013; Karlamangla et al. 2009; Piccinin et al. 2013; Zahodne et al. 2011). However, education is a robust proxy of cognitive reserve, reflected in the fact that brain pathology may be more substantial in high-educated individuals before decline is visible (Bennett et al. 2003), and education has shown to compensate negative effects of occupational solvent exposure (Sabbath et al. 2012).

8.2.4 Adult Work Environment

For a review on the associations between work-related determinants and old age health and physical functioning, see Kulmala and von Bonsdorff (2014). Here, the focus is on how characteristics of the adult work environment relate to the accumulation of cognitive reserve and later-life cognitive function. An important factor determining the possibility of increasing cognitive reserve in the work environment is type and complexity of occupation. Most evidence on the adult work environment comes from studies of adult socioeconomic status, whereby occupation has been shown to have more substantial effects on later-life cognitive function than other SEP indicators such as income or wealth (Lee et al. 2003; Cagney and Lauderdale 2002). Reciprocal associations between occupation and cognitive function seem highly likely, and Schmidt and Hunter (2004) make the case that general mental ability is essential for occupational attainment and job performance. Individuals with higher cognitive function attain higher grade occupations, are given more responsibilities, may have promotions and more training, and may stay longer in the work force. However, in longitudinal analyses, controlling for early-life cognitive abilities and

education, evidence has been accumulated that work characteristics indeed influence cognitive function at later ages. First, in general analyses of *occupational type* without differentiating complexity levels, higher occupational grades have been shown to relate to cognitive level, but not cognitive change over time (Jorm et al. 1998). Occupational level has been shown to be related to risk of dementia (Bickel and Kurz 2009; Li et al. 2002). In line with these findings, there is evidence that longer employment is associated with a delay in the onset of Alzheimer's disease (Lupton et al. 2010). Second, convincing evidence exists for the association of *occupational complexity* and later cognitive function. Occupational complexity is conceptualized as "complexity with people, data, and things" (e.g., Andel et al. 2006). Low complexity has been shown to partly relate to lower cognitive function and cognitive impairment (Andel et al. 2006; Finkel et al. 2009; Kröger et al. 2008). Similarly, training opportunities, higher self-rated effort, and higher mental stimulation were linked to better cognitive performance and more favorable change over 10 years (Marquié et al. 2010). In some studies, variation in cognitive performance by level of complexity was explained by educational differences, and only the highest levels of occupational complexity were predictive of cognitive impairment independent of educational level (Karp et al. 2006). However, Hauser and Roan (2007) show that after controlling for adolescent cognitive ability, occupational complexity is still linked to cognitive function (see also Richards and Sacker 2003). Furthermore, Potter et al. (2008) find an interaction between intellectual demands of work with early adulthood cognitive abilities, showing that individuals in the lower range of cognitive abilities in earlier life stages benefit most from intellectually demanding work.

Psychosocial work characteristics are also predictive of cognitive function. Longer exposure to high job strain and shorter exposure to active jobs were associated with lower scores in most of the cognitive performance tests such as verbal memory and inductive reasoning; however, these associations disappeared with adjustment for employment grade (Elovainio et al. 2009a). Investigating high strain jobs defined by long working hours, Virtanen et al. (2009) found that compared with working 40 h per week at most, working more than 55 h per week was associated with lower cognitive function.

Considering adult work environment over the life course, it seems fruitful to take into account time off work and which activities are performed during employment gaps, because they may have potential to increase cognitive reserve. In a recent paper, we explored the association of time away from work, i.e., employment gaps, with later-life cognitive function. Investigating cognitive trajectories over a 2-year interval, there was evidence that working-life training and maternity spells are related with lower aging-related decline, indicating that activities performed during employment gaps may increase cognitive reserve (Leist et al. 2013).

8.2.5 Social Mobility

Multiple socioeconomic risks (education, income, wealth, and occupation) have a combined effect on cognitive impairment in older adults (Lee et al. 2010). Recent studies have not only considered static indicators of SEP at different points in the life

course, but trajectories from less to more advantaged SEP and vice versa over the life course, termed upward and downward social mobility. In these investigations, there is evidence for differences in cognitive function depending on social mobility. In two studies, childhood SEP, adult SEP, and social mobility were related to cognitive function at later ages, with upward social mobility resulting in more favorable outcomes than downward social mobility, or low SEP sustained over the life course, respectively (Turrell et al. 2002; Haan et al. 2011). However, until studies are available that can take into account differences in cognitive function before the onset of social mobility, it cannot be ruled out that—perhaps subtle—differences in cognitive function, leading to more or less social upward mobility, account for these findings.

8.2.6 Leisure Activities

Reviews on how health behaviors such as smoking, alcohol consumption, and overweight relate with vascular risk factors and later-life cognitive impairment can be found elsewhere (Breteler 2000; see Qiu (2014) for a review of lifestyle factors and dementia, Herghelegiu and Prada (2014) on the association of diabetes, metabolic control, and cognitive function, and Dahl Aslan (2014) for a review on obesity, cognitive aging, and dementia). Here, the focus is on the potential of leisure activities to increase cognitive reserve. Leisure activities have social, physical, and intellectual components, which may provide benefits both to brain reserve (i.e., hippocampal size) and cognitive reserve by resulting in functionally more efficient cognitive networks (Scarmeas and Stern 2003). Reciprocal associations between leisure activities and cognitive function seem possible (Hultsch et al. 1999), but newer evidence suggests that leisure activities contribute to cognitive function and not vice versa (Ghisletta et al. 2006). Dependent on the kind of conceptualization, it is often not clearly distinguishable if social, physical, or intellectual components of the leisure activity contribute to cognitive function, although all components seem to equally contribute to lowering dementia risk and be more beneficial if two or all components were present over a 6-year interval (Karp et al. 2006). The three components of leisure activities will be outlined below.

8.2.6.1 Social Activities

Social participation or integration, measured by the number of social ties or the social nature of reported activities have been found to affect adult cognitive development. Indicators of social integration, i.e., the presence of a spouse or presence of social ties, have been shown to decrease risk of dementia (Fratiglioni et al. 2004; Håkansson et al. 2009). Of particular interest are longitudinal studies which aim at identifying causal relations. Here, social activities and social ties have been found to be associated with a reduced risk of decline from mild to moderate-to-severe impairment or lower aging-related decline in normal cognitive function, respectively (James et al. 2011; Bassuk et al. 1999). Similarly, another study found evidence for social integration influencing cognitive function, but did not find reciprocal effects of cognition on social integration (Ertel et al. 2008).

8.2.6.2 Physical Activities

Physical activity during leisure time provides large health benefits and is associated with lower brain pathology (Gordon et al. 2008; Gow et al. 2012). Consequently, it has been shown that physical fitness, assessed by grip strength, 6-m walk time, and lung function at the age of 79 is associated with better cognitive function, after adjustment for cognitive ability during childhood (Deary et al. 2006). As more indirect measures of physical fitness, many studies have found evidence for a contribution of physical activities to better cognitive function (Middleton et al. 2010; for a review, see Kramer et al. 2006). Here, physical inactivity has been found to be predictive of worse cognitive function over 7 years, while the reverse was not found (Elovainio et al. 2009b).

8.2.6.3 Intellectual and Cognitive Activities

First, cognitive activities such as reading a magazine or playing card games have been shown to be associated with cognitive function (Wilson et al. 2012b) and there is evidence that engagement in political, mental, and the so-called sociocultural activities predicts better cognitive scores over a 10- and 20-year interval, respectively (Kåreholt et al. 2011; Marquié et al. 2010). Intellectual and cultural activities have been found to moderate the education-cognition association (Soubelet 2011). Sachdev et al. (2013) found that the number of current mental activities and openness to experience predicted reversion from Mild Cognitive Impairment to normal cognitive scores 2 years later. However, considering trajectories of cognitive function before and after the onset of dementia, mentally stimulating activity in old age appears to compress the cognitive morbidity associated with Alzheimer's disease by slowing down cognitive decline before dementia and hastening it thereafter (Wilson et al. 2010).

Assessments of current cognitive activity level can be biased by current cognitive function, as individuals with poorer cognitive function may have more difficulties in successfully engaging in cognitively stimulating activities. As Ennis et al. (2013) show, the costs of cognitive activity during memory-search tasks increase with age in adulthood and these costs influence individuals' willingness to engage in demanding cognitive activities. Examining the bidirectional associations between cognitive activity and cognitive function, Wilson et al. (2012b) provide evidence that the level of cognitive activity in a given year predicted a global indicator of cognitive function in the following year, but the reverse was not true: the level of global cognitive function did not predict the subsequent level of cognitive activity. Considering possible memory bias of retrospective assessment of earlier cognitive activity, later-life intervention studies are more suited to investigate the effects of cognitive exercise on preserving and enhancing cognitive function. Jones et al. (2011) review the literature and conclude from experimental evidence in humans that even older adults can benefit from training in basic cognitive abilities, such as speed of processing training, which has been shown to produce immediate improvements with maintained benefits for at least 2 years (Ball et al. 2007; for a review of training effects on cognitive function, see Grönholm-Nyman 2014).

8.3 Contextual Factors

Cognitive function of populations is to some extent influenced by context. Context ranges from family, neighborhood, and school environment to country-specific laws on schooling, unemployment benefits, parental leave benefits, entitlement to leave the workforce (retirement), and others. Most studies investigating later-life cognitive function focus on national samples due to multiple sources of variation if samples of different countries are included, such as language, level of economic development, historical influences and composition of cohorts in terms of educational attainment, socioeconomic status, and others. Therefore, on the country level, variation in cognitive test scores in older adults has rarely been investigated (Langa et al. 2009; Skirbekk et al. 2012). Attempts to investigate specific contextual factors, i.e., temporal or regional variations in state-level schooling laws, have been more promising. In the following, research on neighborhood socioeconomic status, schooling laws, retirement policies, and economic situation during different stages of the life course will be outlined.

8.3.1 Neighborhood Socioeconomic Status

Recent research has linked neighborhood socioeconomic status (SES) to cognitive function on an aggregate level, usually with multilevel studies. Demonstrating life-course cumulative disadvantage, Aneshensel et al. (2011) show that neighborhood socioeconomic disadvantage has an especially large negative impact on cognitive functioning among persons who are themselves poor. Without assessing actual access to resources or exposure to stressors, one can only speculate about the driving forces behind the association between neighborhood socioeconomic status and cognitive function. Neighborhood socioeconomic status has often been used as a proxy for a multitude of neighborhood characteristics, such as neighborhood educational level, institutional resources, and recreational facilities that are not easy to disentangle.

Some studies have conceptualized specific mechanisms through which neighborhood SES may operate, of which one is neighborhood educational level (Wight et al. 2006). Access to health-related community resources seems to lack explanatory power for the difference in cognitive function associated with neighborhood deprivation (Lang et al. 2008). Using data of a representative survey of community-dwelling adults in the city of Chicago, Clarke et al. (2012) show that availability of neighborhood resources may play an important role in the association of neighborhood SES and cognitive function: effects of neighborhood SES on cognitive function act in part through a greater density of institutional resources (e.g., community centers) that promote cognitively beneficial activities such as physical activity. However, effects were restricted to white respondents, which may be due to the fact that language or cultural barriers may prevent access to opportunities offered within these institutions for non-Caucasian Americans. There is no convincing evidence yet that longer residence in low SES neighborhoods additionally worsens cognitive

function (in the sense of a dose–response relationship; see Shih et al. 2011; Clarke et al. 2012) and no relation of neighborhood SES with cognitive decline over time (Al Hazzouri et al. 2011).

To conclude, the study of associations between neighborhood characteristics and later-life cognitive function are certainly at the very beginning. It is important to consider if neighborhood SES can indeed be an unbiased predictor of cognitive function: Individuals choose a neighborhood near their workplace, which reflects different occupational levels, near their family, educational institutions of their children, or a neighborhood with perceived similar SES as themselves. Reputation of schools, housing prices, geographic location, and ethnic composition of the neighborhood all indicate SES level, which may attract individuals with matching attributes. Neighborhood composition may to a large extent be due to self-selection.

8.3.2 Schooling Laws

The impact of contextual factors on later-life cognitive function has impressively been shown from the investigation of state schooling laws, i.e., the number of years of compulsory schooling as a natural experiment influencing cognitive reserve of cohorts. A positive effect of length of compulsory schooling with cognitive function has been shown for the USA (Glymour et al. 2008a), England (Mazzonna and Banks 2011), and six European countries from the Survey of Health, Ageing and Retirement in Europe (SHARE) (Schneeweis et al. 2012). Indirect evidence from state-level education on cognitive function comes from a study of Glymour et al. (2011), investigating the geographic distribution of dementia mortality in the USA. Birth in the Stroke Belt, a southeastern region in the USA consisting of 11 states, has been shown to be associated with risk of later-life stroke and is also associated with increased risk of dementia mortality. The authors refer to the finding that childhood disadvantage, such as extreme poverty and inadequate nutrition, as well as region of residence predict adult dementia. In particular, birth in the southern states of the USA is an indicator of childhood disadvantage, especially for older African-Americans, as Stroke Belt birth is almost certainly associated with lower quantity and quality of education (Glymour et al. 2011).

8.3.3 Retirement

Retirement is certainly a transition that can be investigated from an individual-level perspective, i.e., how does the experience of retirement shape health and cognitive function in later life? However, health, cognitive function, social network, and earnings may to some extent determine the withdrawal from the labor force, which makes findings inconclusive in terms of the actual causal chain. In order to investigate the consequences of retirement, it is useful to use instrumental variables approaches, i.e., to use

variables that are related with the actual variable under consideration, in this case the transition to retirement, but which cannot be influenced by personal factors, such as national retirement policies, in order to circumvent the problem of endogeneity.

The disuse (or "use it or lose it") hypothesis argues that with retirement, individuals lose mental stimulation at work and experience a decrease in cognitive performance. Evidence for this hypothesis mostly comes from studies showing that retirement goes along with a decrease in cognitive function (Roberts et al. 2011; Mazzonna and Peracchi 2012). Reverse causation (i.e., low cognitive function leading to retirement) can be ruled out, as variation in pension, tax, and disability policies explain most variation across countries in average retirement rates (Rohwedder and Willis 2010). However, there is no clear evidence for a dose–response relationship, i.e., the duration of retirement is not clearly associated with level of cognition (Coe et al. 2012).

8.3.4 Economic Situation at Country Level During Different Stages of Life

An interesting recent development in the investigation of life course influences of cognitive reserve is the hypothesis that economic fluctuations may provide individuals with more or less beneficial conditions to enrich cognitive reserve. Evidence is still sparse, but considering possible public health implications, the investigation of how economic conditions influence cognitive function may be fruitful in order to identify individuals at risk of cognitive decline earlier in the life course.

Cognitive reserve could be influenced via a biological pathway from (mal)nutrition to vulnerability to cognitive decline. Van den Berg et al. (2010) show that there are interaction effects of being born during a recession and later negative life events, which in combination lead to adverse outcomes. These later-life events which turned out to be influential were stroke, surgery, death, and illness of a friend. Another suggested pathway from economic fluctuations in adulthood to later-life cognitive function is via the work environment. The economic situation during working life, characterized by economic boom and periods of recession, may provide individuals with more or less stable employment trajectories and with varying degrees of occupational complexity, lifetime earnings, and wealth, which may in turn promote or decrease cognitive reserve. In a recent paper, we identified economic recessions in 11 European countries during respondents' working ages with historical annual data on fluctuations in Gross Domestic Product per capita for each country and related these to both respondents' work histories and later cognitive function assessed with SHARE. We found that recessions during later working life were negatively associated with cognitive function in men, whereas recessions during early adulthood were negatively associated with cognitive function in women. Among men, recessions in later mid-adulthood (ages 45–49) influenced risk of being laid-off, whereas among women, recessions during early adulthood led to working part-time and higher likelihood of downward occupational mobility,

which were all predictors of worse later-life cognitive function (Leist et al. 2014). Future studies may help in clarifying if these findings indeed reflect a true causal chain from contextual economic conditions to later-life cognitive function.

8.4 Conclusion and New Developments

Some recent developments in the research on cognitive function deserve to be mentioned here. First, newer theoretical frameworks suggest that cognitive and emotional skills are developed simultaneously over the life course (Richards and Hatch 2011). This is in line with recent shifts in social inequalities research from social to personal factors explaining later-life health outcomes (Mackenbach 2010), and some evidence pointing to associations of personal factors with later cognitive function (Sachdev et al. 2013; Wilson et al. 2013). A newer line of research tries to link life events, as greater or lesser chronic stressors, to later cognitive function. However, the investigation of single, several, or summary measures of life events have not provided conclusive evidence on how life events are linked to trajectories of later cognitive function (Tschanz et al. 2012; Rosnick et al. 2007; Comijs et al. 2011; Deeg et al. 2005).

There is vast evidence that the concept of cognitive reserve is useful in conceptualizing enrichment effects on cognitive development. Cognitive function is shaped across the life course and modifiable through individual behavior, but also through characteristics of the work and social environment. A stable finding seems to be the fact that normal cognitive function declines slower with more favorable conditions, but after onset of dementia or cognitive impairment, cognitive function rapidly declines. With regard to the association of early-life conditions with later-life cognitive function, it should be the subject of future research to investigate the possible mechanisms in more detail. Whereas some factors have large and consistent effects on cognitive function, such as years of education, others, such as income, have in only a few studies shown associations with later-life cognitive function. Furthermore, to date, there are only speculations in whether and how social and behavioral factors can indeed override biological effects of aging. Considering contextual influences on cognitive function, more evidence is needed to validate possible associations and to find out more about mediating pathways between contextual factors and later-life cognitive function. Ideally, findings on life course influences on later-life cognitive function can be used to promote cognitive reserve in childhood; for example, increasing the level of schooling at the population level seems a worthwhile strategy—and, in later life, to identify and provide interventions for individuals at risk of cognitive decline.

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Chapter 9
Obesity, Cognitive Ageing, and Dementia: The Usefulness of Longitudinal Studies to Understand the Obesity Paradox

Anna Dahl Aslan

9.1 Obesity as a Global Health Problem

Obesity is a global health problem that has reached epidemic proportions (World Health Organization 2000). It is estimated that worldwide approximately one billion adults are overweight, and an additional 475 million are obese (International Obesity Taskforce 2013). In Europe, approximately 60 % of the adult population is either overweight or obese (Hedley et al. 2004; Visscher et al. 2000). Obesity is not only associated with increased risk of physical diseases such as cardiovascular disease, type 2 diabetes mellitus, and cancer, but also with psychological difficulties such as low self-esteem and depression. During the last decade, an increasing focus has been put on the potential influence of obesity on cognitive ageing and dementia. Given the high incidence of obesity in the population, even small negative effects of obesity on cognitive ageing and dementia risk might have a large impact on public health.

9.2 Aims

In this chapter, current knowledge about the association between obesity, cognitive ageing, and dementia will be discussed. However, as there are already several systematic reviews covering both the association between obesity and cognitive functions (Dahl and Hassing 2013; Smith et al. 2011; Sellbom and Gunstad 2012),

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as well as obesity and dementia (Anstey et al. 2011; Gorospe and Dave 2007; Beydoun et al. 2008; Luchsinger and Gustafson 2009; Gustafson 2006; Barrett-Connor 2007), the aim of this chapter is not to be another systematic review. Instead, the focus will be on understanding the shift in association that often is reported. Specifically, midlife (generally defined as the time span between the ages of 40–65) obesity is often associated with an increased risk of cognitive ageing and dementia. The association between late life (generally 65 years of age and older) obesity, cognitive functioning, and dementia is more inconsistent, but a number of studies report that being overweight or being obese in late life is associated with better cognitive function and/or lower risk of dementia. This shift in association, also often reported for mortality, is referred to as the obesity paradox. This chapter aims to unravel this shift in association in particular by evaluating findings from studies with a longitudinal design. However the discussion will first provide a brief overview of some of the core concepts in this chapter: obesity, cognitive ageing, and dementia.

9.3 Obesity

Body fat is usually assessed with anthropometric measures, such as body mass index (BMI), waist circumference, waist–hip ratio, and skinfold thickness. The most common way to assess body fat is with BMI, calculated as weight in kilograms divided by height in meters squared. The underlying assumption of BMI is that most of the variation in weight is due to variation in fat mass. BMI is usually categorized according to the World Health Organization's standard: underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI ≥ 30.0) (World Health Organization 1995). Overweight is associated with increased health risks and not least with an increased risk of becoming obese; obesity is defined as a state in which excess body fat has accumulated to affect health in a negative way (Kopelman 2000). Today, the same BMI recommendations are given to young and old people, and males and females in the Western world.

9.4 Cognitive Ageing

A decline in memory and thinking abilities is one of the main fears of older people and their relatives. Indeed, intact cognitive function is crucial to maintain health, quality of life, and survival in old age. Although the main threat to cognitive function in late life is dementia (which will be discussed below), almost all older people experience cognitive decline to some extent. This age-related change is usually referred to as cognitive ageing. Cognitive functions can be divided into different abilities, such as attention, processing, organization, storing, and retrieval of information. Some of these cognitive abilities are considered more sensitive to ageing

than others. In general, fluid abilities such as processing speed (how fast you process information) are considered to be age sensitive, i.e., decrease at a faster rate with increasing age. Crystallized abilities, such as verbal abilities (to understand written and spoken language), are less age sensitive, and are even considered to decline at a later stage than most other cognitive domains. Further, some memory domains are more age sensitive than others, such as episodic memory, i.e., the ability to remember events that have occurred in the past, while short-term memory (like the ability to repeat a telephone number) seem to remain rather stable.

It is common that older people themselves complain that their memory has become worse in old age or that they do not process information as fast as they used to. However, there are large between-person differences. Some people show a steep decline, some stay fairly constant, and some even improve (Wilson et al. 1999; Wilson et al. 2002). A main aim within the field of ageing research has been, and still is, to identify factors associated with reduced or slower cognitive ageing, so that preventive actions can be taken. As such a factor, obesity has received increasing research interest particularly during the last decade.

9.5 Dementia

Dementia is a common disease in late life, associated with dependency, institutionalizations, and death. It is estimated that 6–10% of people aged 65 years and above are affected by dementia (Hendrie 1998), and that prevalence rates increase with increasing age. Among 90 year olds it is estimated that about one out of two has severe cognitive deficits. Dementia causes a gradual and progressive decline in memory, as well as impairments in other cognitive functions such as disturbance in executive functioning (like planning and problem solving). In the long run these disturbances lead to the inability to manage daily living (American Psychiatric Association 2000).

The most common type of dementia is Alzheimer's disease (AD) followed by vascular dementia (VaD), wherein AD accounts for about 50–70 % of all dementia cases. The biological hallmark of AD is the accumulation of amyloid β in the brain which causes synapse disruption and neuronal death. VaD accounts for about 20–30 % of all dementia cases. It is a heterogeneous disorder caused by cerebrovascular complications ranging from small vessel ischemic disease to stroke. Although it might seem that AD and VaD are two separate diseases, there is often an overlap in the pathologies, and AD pathology is considered to increase the risk of vascular injury and vice versa (Craft 2009). Likewise, it might be very hard to differentiate between age-related cognitive changes and cognitive change that is caused by dementia processes, both in clinical practice and in research.

Given that there currently is no cure for dementia, the identification of risk factors that might be modifiable has received great research interest. As for cognitive ageing research, during the last decade obesity has received attention as a potential risk factor for dementia, both of vascular origin and AD.

9.6 Current Knowledge About Obesity, Cognitive Ageing, and Dementia

Current systematic reviews (Smith et al. 2011; Dahl and Hassing 2013) jointly confirm that there is an association between higher BMI in midlife (in general before the age of 65 years) and lower cognitive abilities, across domains in late life. However, in a number of studies where BMI is assessed in late midlife and especially in late life, the picture is not clear-cut. Some studies show that people who are underweight and/or normal weight perform at a lower level or have a less steep cognitive decline compared with people with higher BMI, either cross-sectionally or prospectively (Kuo et al. 2006; Brubacher et al. 2004; Buchman et al. 2005; Sturman et al. 2008). In contrast, two cross-sectional studies, one based on Spanish data and the other on a population-based Scottish study, indicate that older obese persons had lower cognitive performance across a wide span of cognitive domains, compared to their normal weight counterparts (Benito-Leon et al. 2013; Corley et al. 2010). Furthermore, several studies report a U-shaped association between late life BMI and late life cognitive functions, i.e., that both persons with low BMI and persons with high BMI in late life have lower cognitive functions (Sturman et al. 2008; Dahl et al. 2013b; Sabia et al. 2009).

Several reviews and meta-analyses (Beydoun et al. 2008; Gorospe and Dave 2007; Gustafson 2006; Anstey et al. 2011; Barrett-Connor 2007) also show that obesity in midlife is associated with an increased risk of dementia—both of vascular origin and AD. As for the association between BMI and cognition in late life, the available evidence on associations between late life BMI and dementia also shows contradictory results. Many studies report that people who are underweight and/or normal weight in late life have an increased risk of dementia (Dahl et al. 2008; Atti et al. 2008; West and Haan 2009; Tolppanen et al. 2013; Kerwin et al. 2011), while others indicate a decreased risk of dementia (Hayden et al. 2006; Gustafson et al. 2003). Further, one study report a J-shaped association, where those with lower BMI had an increased risk, but those with higher BMI had an exponentially increased risk (Luchsinger et al. 2007).

It is not clear when this shift starts to happen but in the Atherosclerosis Risk in Communities (ARIC) Study, where the participants had a mean age of 59 years at the age of assessment of BMI, there was no association between higher BMI and cognitive change (Knopman et al. 2009). Further, in the Honolulu Asian Ageing Study (HAAS) higher weight in late midlife (age 46–68 years) was not associated with an increased risk of dementia (Stewart et al. 2005). Hence, it is likely that this shift in association starts in late midlife. Reasons for this shift in association will be discussed below.

9.7 Effect of Obesity on Cognitive Change

In all, except from findings from the Swedish Adoption/Twin Study of Aging (SATSA), which is the currently published study with the longest follow-up time and richest assessment of cognitive abilities (Dahl et al. 2010, 2013b), the evidence

that midlife obesity is related to steeper cognitive decline is weak (Dahl and Hassing 2013). Specifically, studies with shorter follow-up time and fewer assessments of cognitive abilities generally report weak associations between midlife obesity and cognitive decline. Negative effects of obesity are also often only found in sporadic tests or the effects disappear when confounding factors are controlled for.

However, it should be highlighted that there is evidence indicating that there might be a stronger effect of midlife obesity on change in verbal abilities (Dahl and Hassing 2013). Three studies, SATSA (Dahl et al. 2013b), OCTO-twin (Hassing et al. 2010), and Vieillissement, Santé, Travail (Aging and Health at work; VISAT) (Cournot et al. 2006), showed an effect of midlife obesity on cognitive decline in verbal abilities. Given that verbal abilities represent the cognitive domain considered to be most resistant to ageing (Schaie 2005; Finkel et al. 2003), it could be hypothesized that it might be easier to pinpoint factors (such as obesity) associated with changes in this domain. The association between midlife obesity and steeper cognitive decline in tests measuring verbal abilities needs further evaluation as decline in verbal ability might be an indication that something is seriously wrong, as changes in this cognitive domain are usually small during the normal ageing process.

Few studies have evaluated how BMI affects cognitive change after the age of 65 years. Results from the Cardiovascular Health Study (mean age 73 years at baseline) showed that, on average, those who were obese had a slower cognitive decline over an 8-year period of follow-up compared to normal weight participants in modified Mini-Mental State Examination (a test of general cognitive ability), and the Digit Symbol Substitution Test (a test of perceptual speed) (Luchsinger et al. 2013). In a similar vein, findings from the Chicago Health and Aging project (including persons 65 years and older at baseline) showed that persons who gained BMI in late life had less steep decreases in cognitive functions over a 6-year period (Sturman et al. 2008). In SATSA, including persons aged 50–75 years of age at baseline (mean age 61 years), late life obesity was associated with decline in verbal abilities over a period of 20 years but not with declines in spatial abilities, memory, and processing speed (Dahl et al. 2013b). Again, the association between late life obesity and cognitive functioning is not clear.

9.8 Unraveling the Obesity Paradox with Longitudinal Data

To understand these contradictory results which suggest that higher BMI in midlife is a risk factor for lower cognitive functions and dementia in late life while the opposite has often been reported in late life, several aspects need to be considered. These aspects include the interference of preclinical dementia on both BMI and cognitive abilities, weight changes and weight histories, age of assessment of BMI and cognitive functions, and the follow-up time. These issues will be discussed in the following paragraphs.

9.8.1 Interference of Preclinical Dementia Symptoms

The most common explanation for the diverging results in midlife and late life is the interference of preclinical dementia symptoms. Both weight and cognitive functions are believed to decline more than 10 years before the clinical onset of dementia (Knopman et al. 2007; Stewart et al. 2005; Arnaiz and Almkvist 2003). Therefore, in cross-sectional studies and in studies with short follow-up time it cannot be excluded that reported findings are due to preclinical dementia. The older the sample is at baseline the higher is the risk that preclinical dementia affect the results, as the prevalence of dementia increases with advancing age.

A surprisingly large number of studies within the field of BMI and cognitive ageing research do not consider clinically diagnosed dementia as a potential confounder of the association, or at least do not report it. In those studies where dementia is considered, different approaches are used to control for the influence of dementia. Two commonly used approaches are to exclude everyone diagnosed with dementia from the study and to exclude the cognitive scores either at the time of clinical diagnosis of dementia or some years before the clinical diagnosis. If the first approach is used, it is common to report the findings both including and excluding persons with dementia. Sometimes a cognitive test score, usually a score below 25 on the Mini-Mental Examination Test (MMSE), is used as a proxy of dementia (Dahl et al. 2007). A third approach is to control for dementia prevalence. Studies that use these approaches yield inconsistent results. Excluding or including persons with dementia, when evaluating the BMI and cognitive ageing association, did not affect significantly the estimates or associations in a study based on the SATSA, evaluating midlife BMI in relation to general cognitive ability based on 11 cognitive tests (Dahl et al. 2010). However, in the Chicago Health and Aging project, the protective effect of higher BMI on cognitive decline over a 6-year period did not remain significant when those with an MMSE score below 25 were excluded. Future studies that report the association between obesity and cognitive ageing, both including and excluding persons with dementia, are warranted.

9.8.2 Weight Changes

Another way to understand how dementia might affect the association between BMI and cognitive ageing, and BMI and dementia, is to consider *weight changes*. As already mentioned, there is compelling evidence that weight decline/decline in BMI is associated with incident dementia and this might be accelerated the years before the clinical diagnosis (Stewart et al. 2005; Knopman et al. 2007). But to understand if weight decline drives the association between low BMI, cognitive ageing, and increased dementia risk, both level of BMI and change in BMI need to be considered in the same model. This kind of analysis was performed on Swedish population-based longitudinal data. Initial analysis showed that being underweight (in this case a BMI < 20) in late midlife (mean age 61 years) was associated with lower cognitive ability in late life. However, when weight change from early to late midlife was taken

into account, this association was no longer significant (Dahl et al. 2013b). Instead, it was the persons who had lost weight from early to late midlife that had a lower cognitive test performance. Similarly, in the Finnish Cardiovascular risk factors, Aging and Dementia (CAIDE) study the association between low BMI and increased dementia risk was attenuated when weight decline was controlled for (Tolppanen et al. 2013). However, it should be mentioned that the association between low BMI and increased dementia risk was not particularly strong from the beginning in the CAIDE study. These findings indicate that weight change might shed light on the obesity paradox, but the findings need to be replicated in other studies.

9.8.3 Weight Histories

Although it is pretty common to lose weight during the last decades of life, older individuals are a very heterogeneous group also in terms of *weight histories*. Some might have maintained stable weight (at different levels) their whole life, some might have declined or increased at different time points of life. Knowledge about these weight histories is relevant, as it has been suggested that being overweight and/or obese over longer periods of time is more dangerous with regard to risk of cardiovascular disease and mortality than being overweight and/or obese at single time points or for shorter periods of time. Few studies are able to take weight history into account, but findings from the SATSA and from the Whitehall II study show that being overweight/obese over longer periods of time seem be associated with lower cognitive functions than being overweight/obese at a single time point (Dahl et al. 2013b; Sabia et al. 2009). However, it is important to note that being overweight/obese over longer periods of time was not associated with steeper cognitive decline, just with lower mean level performance (Dahl et al. 2013b). Neither is there strong evidence that *weight gain* across midlife would be associated with lower cognitive function. For example, no association between weight gain and lower cognitive functions were reported in SATSA (Dahl et al. 2013b). In VISAT, weight gain was only associated with lower attention, but not with processing speed or verbal abilities (Cournot et al. 2006). However, there are still too few studies on this topic to draw any firm conclusions.

9.8.4 Follow-up Time

Further, the *follow-up time* between assessments of body fat, cognitive functions, and dementia needs to be considered. According to a meta-analysis, the average follow-up time in studies focusing on late life obesity and dementia is only 7 years (Anstey et al. 2011). Therefore, it cannot be excluded that obesity might be a risk factor of dementia over a longer period of time. Results from the Gerontological and Geriatric Population Studies in Gothenburg (H70), with a follow-up time of 18 years, indicate that late life obesity is a risk factor of Alzheimer's disease (Gustafson et al. 2003). Similarly, in SATSA with over 20 years of follow-up, late life obesity

was a risk factor for all-cause dementia (Dahl et al. 2013a). No other study has assessed late life obesity and dementia risk over 20 years. However, in a French study, low BMI in late life predicted the onset of dementia within 5 years of follow-up, but did not predict dementia over the total follow-up period of 8 years (Nourhashémi et al. 2003).

9.9 Direction of the Association

Although there is strong evidence that there is a link between being obese in midlife and lower cognitive function in late life, the question about causality needs to be raised. This is especially relevant since the evidence of a negative effect of obesity on cognitive ageing is weak and inconsistent (Dahl and Hassing 2013). However, support for obesity possibly causing cognitive ageing comes from studies showing that persons who are obese over long time periods show lower cognitive functions than persons who are obese over shorter time periods (Sabia et al. 2009; Dahl et al. 2013b).

Several studies have linked low cognitive function in childhood to an increased risk of becoming obese in young adulthood, midlife, and even in late life (Chandola et al. 2006; Lawlor et al. 2006; Corley et al. 2010). A review study suggests that especially low executive functions in childhood are associated with a higher risk of becoming obese (Smith et al. 2011). In addition, research using cross-sectional analyses in midlife (Cournot et al. 2006; Dore et al. 2008) indicated that, in some cases, higher BMI is associated with lower cognitive test performance. However, there are also contradictory results. In a study of one million Swedish young-adult men, high BMI was reported to be only weakly inversely associated with intelligence (Batty et al. 2009).

Further support for the theory that the association between obesity and cognitive functions has been present since early life comes from the Lothian Birth Cohort 1936 (Corley et al. 2010). In this study, the negative association between late life obesity and cognitive ability almost completely disappeared when controlled for early life cognitive ability; it only remained significant for verbal ability. In contrast, two reports on midlife BMI and late life cognitive functions based on Swedish data showed that when verbal ability was used as a proxy of early life cognitive ability, the association between midlife obesity and cognition was not substantially attenuated (Hassing et al. 2010; Dahl et al. 2013b). In all, these findings indicate that the question about the causality remains to be elucidated, and might likely be bidirectional.

9.10 Causal Pathways Between Midlife BMI and Cognitive Decline and Dementia

In the following, potential causal pathways between midlife weight and later-life cognitive decline and dementia are presented.

9.10.1 Cardio-Metabolic Pathways

Cardio-metabolic disorders are a potential pathway from midlife obesity to low cognitive function and greater risk of dementia. It is well established that obesity is associated with an increased risk of cardio-metabolic factors such as hypertension and type 2 diabetes mellitus (see Herghelegiu and Prada 2014), as well as that cardio-metabolic factors are risk factors of steeper cognitive ageing and a greater dementia risk (see Qiu 2014). Almost all studies with a focus on obesity, cognitive ageing, and dementia do control for the prevalence of cardio-metabolic factors to some extent. However, the association between being obese in midlife, cognitive ageing and dementia is generally not substantially attenuated by controlling for cardio-metabolic factors. This holds true either if one or many factors are summed together, or if cardiovascular events such as stroke or ischemic heart attack have occurred (Dahl and Hassing 2013).

However, in some studies the association between midlife obesity and late life cognitive health does attenuate when cardio-metabolic factors are controlled for. For example, in the VISAT study the effect of midlife obesity on cognitive decline became nonsignificant when cardiovascular disease was controlled for (Cournot et al. 2006). Further, in Swedish twin data the association between midlife obesity and VaD was attenuated when cardio-metabolic diseases were controlled for, but not the association between midlife obesity and AD (Hassing et al. 2008).

Despite the fact that cardiovascular disease does not consistently mediate the association between obesity and cognitive ageing, and between obesity and dementia, across studies, it is likely that mechanisms related to cardiovascular disease provide at least one of potentially several pathways between obesity and cognitive ageing. Failures to find mediation effects might partly originate from methodological limitations. For example, undiagnosed type 2 diabetes, hypercholesterolemia, and hypertension are common in the general population (although this should be less common in longitudinal studies where participants generally receive feedback on the health assessment). In addition, the effects of the preclinical phase are usually not assessed, and treatment and treatment adherence are usually not captured. Further, if cardio-metabolic factors are only assessed at baseline, it is possible that the negative effects have not yet occurred and hence the mediating effect might not have been captured.

9.10.2 Inflammatory and Hormonal Pathways

Another proposed causal pathway is through inflammatory processes. Obese persons have higher levels of inflammation than normal-weight persons (Ridker et al. 2003). In longitudinal studies, serum C-reactive protein and pro-inflammatory cytokines like IL-6 have been associated with cognitive decline (Yaffe et al. 2004; Tilvis et al. 2004), and an increased risk of dementia (Schmidt et al. 2002). Studies that can take both fat mass levels and inflammatory processes into account are warranted.

Hormones, cytokines, and growth factors that are produced in adipose tissue are also suggested to be potential pathways. These factors may interact directly with blood vessels (De Michele et al. 2002; Williams et al. 2002) or can probably cross the blood–brain barrier (Lathe 2001) and contribute to disrupting homeostasis in the brain. For example, leptin and adiponectin have been suggested as possible pathways between obesity, cognitive ageing, and dementia (Barrett-Connor 2007).

9.10.3 Lifestyle-Related Pathways

However, there might also be lifestyle-related pathways between obesity, cognitive ageing, and dementia. Obesity might, for example, be caused by lack of physical activity. Both studies with short- and long-term follow-up indicate that physical activity has positive effects on cognitive abilities (Chang et al. 2010; Hamer and Chida 2009). Overall, few studies on obesity, cognitive ageing, and dementia take physical activity into consideration. A couple of studies on midlife BMI and risk of cognitive decline have adjusted for frequency of physical activity (Dahl et al. 2013b; Hassing et al. 2010). In neither of these two studies was the association between midlife obesity and lower cognitive functions substantially attenuated when physical activity was included in the analysis. However, in both these studies the assessment of physical activity was rough and relied on self-report.

Dietary habits also are lifestyle factors that are related to obesity and have been suggested to be linked to increased risk of cognitive decline and dementia (Feart et al. 2009). However, similar to the inclusion of physical activity, few studies have considered both obesity and dietary habits.

9.10.4 Common Genetic Causes

Another alternative would be that there are underlying shared etiologies between obesity and low cognitive function and between obesity and dementia. Both the main variations in obesity and cognitive function are estimated to originate from a genetic disposition (Stunkard et al. 1990; McClearn et al. 1997; Pedersen et al. 1992). Therefore, it is of interest to evaluate whether obesity and cognitive function, as well as obesity and dementia, share a common genetic cause. A Finnish twin study indicates that there is shared genetic variance between obesity and cognitive function (Laitala et al. 2011). The importance of genetic factors as well as early rearing environment for the BMI and dementia association has also been reported in a Swedish study (Xu et al. 2011). Today there is no strong evidence that obesity-related genes such as the fat-associated gene (*FTO*) modify the association between obesity, cognitive ageing, and dementia.

9.11 Weight Decline in the Preclinical and Clinical Stages of Dementia

Most researchers believe that low or declining BMI is a symptom of dementia rather than a true risk factor. The processes that cause people with preclinical dementia to lose weight are complex and most likely multifactorial. Behavioral changes such as forgetfulness, loss of initiative, and the inability to perform complex tasks such as cooking might cause persons with dementia to lose weight. Declining BMI might also be a manifestation of poorer psychological and emotional well-being. Depression is common in the preclinical and early stages of the dementia processes and might include loss of appetite and/or loss of enjoyment of food. There might also be pathological changes that produce an association between weight decline and dementia. For example, changes in olfactory functions is associated with decline in cognitive functions (Finkel et al. 2011) and Alzheimer's disease (Tabert et al. 2005), accordingly, food becomes less appetizing. This has been suggested to be due to changes in brain structures regulating olfactory functions. Changes in other brain structures, such as cingulate gyrus or hypothalamus, can also cause disturbances in weight control (Hu et al. 2002). Atrophy in hippocampus and the medial temporal lobe have also been related to lower weight in AD patients (Grundman et al. 1996).

9.12 Other Anthropometric Measurements of Fat Mass than Body Mass Index

The majority of the studies mentioned in this book chapter assessed obesity with BMI. BMI is often criticized for not adequately differentiating between fat and muscle mass and this is more pronounced among older adults (Jackson et al. 2002). It is known from cardiovascular research that elevated intra-abdominal fat, usually measured by waist circumference and waist-to-hip ratio, is a better predictor of cardiovascular events in midlife than if the fat is more generally distributed across the body. Especially if the causal pathway from obesity to cognitive ageing and dementia goes through cardiovascular events, measures of central obesity should be more strongly associated with cognitive ageing and dementia.

Still, few studies with a focus on cognitive ageing include measures of central obesity, and, in those studies that do, the findings are not consistent. In the Framingham Offspring Cohort higher waist-to-hip ratio was associated with poorer executive function and spatial ability, while higher BMI was not (Wolf et al. 2007). On the other hand, in the Baltimore Longitudinal Study of Aging, higher waist circumference and waist-to-hip ratio were to a smaller extent associated with cognitive ageing than BMI (Gunstad et al. 2010).

When it comes to central obesity and dementia risk, two large studies based on US samples have indicated that measures of central obesity both in midlife and late life are associated with an increased risk of dementia (Whitmer et al. 2005; Kerwin et al. 2011).

Comparing the risk estimates between being centrally obese and being generally obese (i.e., to have a higher BMI) indicated that central obesity was associated with a higher risk of dementia than general obesity. Not very surprisingly those that had both—a high waist circumference and a high BMI—were at the greatest risk of dementia, but also those of normal weight but with an elevated waist circumference had a higher risk of dementia than those with a higher BMI but lower waist circumference (Kerwin et al. 2011). In a Swedish sample only among women, higher waist-to-hip ratio was associated with an increased dementia risk, while BMI was not (Gustafson et al. 2009). In a US study that assessed BMI and waist circumference in older adults, the association between different anthropometric measures and various forms of dementia showed inconclusive results (Luchsinger et al. 2007). Waist circumference was associated with dementia associated with stroke both among young–old and old–old adults, while BMI and waist circumference had less predictive value among old–old adults compared to young–old adults.

In general, these findings indicate that being centrally obese in midlife is associated with an increased risk of dementia. Potentially, measures of central obesity are better predictors of dementia than BMI in midlife, and hypothetically of VaD given the suggested cardiovascular pathway. However, the usefulness of measures of central obesity compared to BMI in late life in relation to cognitive ageing and risk of dementia remains to be elucidated.

9.13 Limitations and Future Directions for Research

There is much to acknowledge in the current literature on obesity, cognitive ageing, and dementia. An increasing number of studies focusing on these associations give a possibility to bring forward scientific understanding. However, some aspects that still remain to be addressed in future research will be addressed below.

In general, those studies which focus on cognitive ageing use a wide range of cognitive tests, with good psychometric properties. Still, there are too few studies to draw any conclusions to which extent obesity is associated with specific cognitive domains. There is also an overrepresentation of studies with short follow-up time that makes it impossible to distinguish between normal cognitive ageing and cognitive decline due to dementia. Surprisingly often is the influence of dementia not controlled for in studies on cognitive ageing.

Obesity is partly caused by several factors that also have been suggested to be associated with increased risk of cognitive ageing and dementia, such as low physical activity and high caloric intake. Further, obesity is associated with many other health states, such as elevated blood glucose levels, type 2 diabetes, high blood pressure, that also have been associated with negative brain health. Although the majority of the studies control for cardiovascular diseases, and sometimes exercise and diet, few studies have studied the combined effect (Anstey et al. 2011). Similarly, there is a need for studies that not only control for these covariates, but also test for moderation and mediation effects. Beyond the inclusion of cardio-metabolic factors, there is also a need for studies that include measurements of inflammatory and hormonal levels.

An essential key to understanding the association between obesity, cognitive ageing, and dementia, and especially the obesity paradox, is the use of longitudinal studies. Due to labor-intensive procedures, long-term commitments and high costs, these kinds of studies are rare. In other words, there is a need for studies with repeated measures of fat mass, cognitive functions, clinical evaluations of dementia that range from childhood to death. The arguments for the usefulness of longitudinal studies have been described and discussed in detail across this chapter, especially in Sect. 9.8, so it will only shortly be repeated here.

First of all, only studies with repeated measures of both fat mass and cognitive function can elucidate the direction of the association, by having access to both measures of obesity and cognitive abilities across the life course. Although it is often assumed that obesity is associated with cognitive ageing, evidence for this is actually rather weak. It is probable that the association is bidirectional. It is also important to have repeated measures to evaluate how and if different weight patterns, such as increased weight or decreased weight, are associated with a higher risk of cognitive decline and dementia. Longitudinal studies would also be able to give a general indication of when during the life course the shift in association appears. This could contribute to insights about what should be considered a healthy BMI at different stages of life. Most likely not only a single assessment of BMI should be considered but also weight changes and weight histories, as well as other measures of fat mass. Even though the current findings based on longitudinal studies show promising results it should be highlighted that they are still few and therefore the conclusions should be interpreted with caution.

Further, although epidemiological data shows strong evidence for an association between higher BMI in midlife and greater risk of lower cognitive functions and dementia in late life, intervention studies need to evaluate whether weight loss in midlife would contribute to improved cognitive functions and a decreased risk of dementia. It is also too early to give any firm conclusions about what should be considered a healthy BMI level in late life when it comes to cognitive function and dementia. However, the current evidence indicates that spontaneous weight decline is not a good sign and this is a phenomenon that is more common in late life than in any other stage during the life course (Dahl et al. 2013c). It is likely that the most healthy weight trajectory is to maintain a stable weight across the life span, although it remains to be proved. If it holds true, the main focus for health recommendations and interventions should be on maintaining a stable weight. If this starts early in life, many of the negative consequences of obesity might be avoided, including the negative effect on cognitive functions and dementia.

9.14 Conclusion

The general pattern indicates that midlife obesity is associated with lower cognitive functions and increased risk of dementia, but there is weak evidence for the effect of midlife obesity on cognitive decline. Further, there is still not enough evidence to draw any firm conclusions about what should be considered a healthy BMI level in

late life in relation to cognitive ageing and dementia risk. However, findings from longitudinal studies indicate that weight changes might contribute to a better understanding of the association between obesity, cognitive ageing, and dementia. Especially, it seems like weight decline both in midlife and late life might be an indicator of worsening cognitive functions and increased risk of dementia. It is possible that the ideal goal should be to maintain a stable weight, and maybe that less focus should be put on BMI level in late life.

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Chapter 10
Models for Predicting Risk of Dementia: Predictive Accuracy and Model Complexity

Blossom Christa Maree Stephan

10.1 Introduction

Dementia is a major global health concern. With an increase in the proportion of older aged individuals with increasing life expectancy, dementia prevalence is predicted to rise. Approximately 0.5 % of the world's total population is said to suffer from dementia, with the number set to grow. In 2010 worldwide dementia prevalence was estimated at over 35 million cases with the disease costing approximately US$604 billion. By 2050 it is estimated that there will be 115 million dementia cases worldwide. A 2-year delay in dementia onset could dramatically affect its prevalence, reducing disease frequency by approximately 20 % (Brookmeyer et al. 1998). The modification of health (e.g., diabetes, midlife hypertension and midlife obesity), lifestyle (e.g., physical inactivity and smoking), psychiatric (e.g., depression) and cognitive (e.g., low education and cognitive inactivity) factors could potentially prevent up to three million Alzheimer's disease (AD) cases worldwide (Ritchie et al. 2010). An important challenge is therefore to identify who will most likely benefit from intervention and risk factor reduction.

However, unlike other disease areas, such as cardiovascular disease, where there has been a proliferation of risk prediction models (e.g., Framingham Risk Scores and QRISK2), that have had a significant benefit for informing treatment decisions, patient outcomes and research (e.g., clinical trial recruitment and the design of prevention strategies) no such risk prediction tools currently exist for dementia. Indeed, a review of the literature by the UK National Screening Committee (in 2003, with updates in 2006, 2009) concluded that there is no evidence-based routine screening program recommended for assessing at-risk or symptomatic AD cases (UK Screening Portal). Committees outside the UK (e.g., US Preventive Services Task

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Force) have also reached similar conclusions. What is needed is a strategic approach to risk score development that would involve a number of steps:

1. Identification of the most predictive risk factors, across age groups, settings, populations and time frames
2. Deviation of a risk score, developed using appropriate statistical methodology, that weighs the value of factors identified in the most parsimonious model
3. Internal model validation
4. External model validation
5. Cost-effectiveness analysis and ethical assessment
6. User/consumer feedback
7. Policy development
8. Implementation (if methodologically sound, beneficial, cost-effective, acceptable, and doesn't lead to inequality)

From a public health perspective, accurate identification of individuals at high risk of dementia will become crucial with dementia initiatives that raise awareness of the disease and the expanding interest in dementia risk minimization (such as the UK "Live Well With Dementia" strategy). From a clinical perspective, accurate identification of high-risk cases will be important as strategies to prevent or delay dementia onset become available and we move towards personalized medicine (e.g., tailoring care to specific characteristics of individuals). From a research perspective, having a model that accurately identifies high-risk cases will be important for identifying targets for intervention and for improving participant selection into dementia trials.

In 2010 a systematic review of the models that have been developed for dementia risk prediction in population-based studies was undertaken (Stephan et al. 2010a). This chapter will build on this review, updating the search and expanding the focus to include the application of cardiovascular risk models within a dementia risk prediction framework.

10.2 Model Evaluation

Decisions about the efficacy of a risk model are typically based on measures of sensitivity, specificity, positive and negative predictive value (PPV and NPV), and the area under the receiver operating characteristic curve (ROC AUC)/concordance (c)-statistic. A description of each of these is provided Table 10.1.

However, while these measures provide an overview of model performance they are not without their problems. They can vary depending on characteristics of the population such as sample size, definition of the outcome, length of follow-up, and prevalence of the disease for which the model is being developed (Ransohoff and Feinstein 1978). Further, measures such as the AUC/c-statistic must be interpreted in light of the methods used to develop the risk model (e.g., treatment of missing data, survivor effects, consideration of competing risks, how continuous risk variables are treated and the number of predictor variables included in the model, i.e.,

Table 10.1 Measures for evaluating risk prediction models

Measure	Description
Sensitivity	Ability of the model to identify those at-risk (e.g., true positive rate)
Specificity	Ability of the model to identify those not-at-risk
PPV	The proportion of individuals classified as high risk who develop the disease
NPV	The proportion of individuals classified as low risk who do not develop the disease
AUC/c-statistic	A marker of discrimination that measures the ability of the risk model to distinguish between who will and will not develop the disease. This measure ranges from 0 to 1, with a score of 0.5 representing risk prediction by pure chance and a score of 1 representing perfect discrimination

general rule is one variable for every ten people with the outcome event). Calculation of ROC curves for censored data without consideration of survivor effects can be misleading, since some individuals had they lived longer could have had the disease. Ignoring competing risks (e.g., associated with death or treatment effects) often leads to incorrect estimation of absolute risk.

What is considered an acceptable vs. unacceptable level of accuracy usually depends on what the model will be used for (e.g., as the basis for intervention/treatment decisions, for insurance, for clinical trial enrolment) and the consequences of an incorrect decision (e.g., exposure to a potentially hazardous treatment in a well subject, a missed opportunity for intervention where available, loss of privileges such as driving in the case of dementia screening, or unwarranted psychological distress associated with positive/negative screen results). Generally, where there is significant risk associated with a positive screen (or missed screen) both sensitivity and specificity would be required to be high. In contrast, where the risk associated with a positive screen is low sensitivity could perhaps be sacrificed in favor of increased specificity. It is important to note that sensitivity and specificity are related such that as one rises the other falls (unless both are at 100 %). As yet, within a dementia risk prediction framework, there are no clear guidelines for determining the minimum cut-off for discriminative accuracy, sensitivity and specificity. In this chapter, similar to the systematic review undertaken on dementia risk prediction models (Stephan et al. 2010a), sensitivity and specificity estimates of <70 %, 70–80 % and ≥80 % will be considered to represent measures of low, moderate and high accuracy, respectively (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and National Institute on Aging Working Group 1998). AUC values 0.9–1, 0.7–0.89 and ≤0.7 will be used to indicate excellent models, good models and models of questionable utility, respectively (Swets 1988).

Risk models must also show good calibration, such that there is agreement between observed and predicted values. Calibration is typically assessed using the Hosmer–Lemeshow Chi-square statistic and its extensions (Hosmer and Lemeshow 2000). Poor calibration is usually found when a model undergoes external validation; that is, the model is tested in a population different from which it was derived. This could be due, for example to differences in population characteristics (e.g., age, disease levels or prevalence of risk factors), whether treatment effects differ across populations and possible heterogeneity in end point definitions such as

more specific and restrictive criteria for disease in some studies. Where calibration is poor (e.g., there is systematic over- or under-estimation of rates of disease) models can be recalibrated to optimize data fit. Recalibration involves recalculating risk scores using data from the new cohort and assessing the applicability of the modified risk functions in the new cohort (for an example of recalibration of the Framingham Stroke Risk (FSR) Score in a French-based sample see: Bineau et al. (2009)).

10.3 Evaluating Incremental Value from New Predictors

Any model developed should be future proof such that as technology changes and novel biomarkers are discovered (e.g., imaging, genetic, circulating) model performance can be re-examined with the addition of new risk variables. The additive effect of a novel risk variable to the discriminative accuracy of a traditional risk model can be tested by statistically comparing the AUCs between the traditional and extended models (e.g., using a Chi-square test). However, changes in AUC estimates are often small in magnitude when models already incorporate powerful risk factors and perform reasonably well. An alternative to calculating the difference between two AUCs is the use of classification measures such as: Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) (Cook 2007, Pencina et al. 2008). NRI incorporates both desirable and non-desirable risk classification (e.g., individuals changing risk categories and their direction of change) for individuals who experience and did not experience the outcome event (Pencina et al. 2012). The IDI is a continuous measure of the NRI (e.g., this measure uses probability differences instead of categories) and quantifies the amount of improved sensitivity without reducing specificity (Steyerberg et al. 2010).

In addition to improved discrimination and risk classification accuracy any new variable must be cost-effective. Any new risk model must also be parsimonious and maintain an optimum balance between accuracy and ease of attaining the risk score.

10.4 Diagnosing Individuals at High Risk of Dementia: Mild Cognitive Impairment

In clinical practice individuals at high risk of dementia are typically diagnosed using criteria for mild cognitive impairment (MCI), defined as an intermediate state between cognitive changes associated with normal aging and those associated with dementia (Matthews et al. 2007). Many definitions for this state exist, including for example amnestic MCI (Petersen et al. 1999, Petersen et al. 2001), cognitive impairment no dementia (CIND) (Ebly et al. 1995), and age-related cognitive decline (ARCD) (American Psychiatric Association 2000). The different definitions vary with regard to the nature and severity of the cognitive impairment (e.g., memory, non-memory or global functioning, cut-off norms for cognitive impairment),

exclusion criteria for functional difficulty (e.g., in Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)), and whether a memory or cognitive complaint, reported by the individual or a significant other, is incorporated into the diagnostic criteria (Stephan et al. 2007). The lack of a consensus definition for MCI results in variability in participant selection making cross study comparison difficult (Stephan et al. 2007, Stephan et al. 2013).

When diagnosed in clinical settings, individuals with amnestic MCI have an annual dementia progression rate of approximately 9.6 % (95%CI: 6.3–13.4 %), with approximately 39.2 % progressing to dementia over 5 years (Mitchell and Shiri-Feshki 2009). In population-based studies progression rates vary across the different MCI definitions and are generally found to be lower than the rates reported in clinical samples (4.9 %; 95%CI: 1.6–9.9 %) (Matthews et al. 2008, Mitchell and Shiri-Feshki 2009). Further, while some MCI cases progress to dementia, others are found to remain stable or revert to normal functioning, particularly when mapped in population-based settings (Matthews et al. 2008). In population settings, when evaluated within a risk prediction framework, predictive accuracy of the many different MCI definitions is generally low to moderate such that no MCI criteria have both sensitivity and specificity over 80 % (Stephan et al. 2010a, b). Therefore, using MCI criteria alone it is not possible to predict with certainty a dementia outcome.

Attempts to improve the predictive accuracy of MCI (and CIND (Ritchie and Tuokko 2011)) have focused on supplementing diagnostic criteria with genetic (e.g., apolipoprotein (APOE) e4 status), cerebrospinal fluid (CSF, a normally clear fluid found in the brain and spine) markers (e.g., amyloid beta 42, total and phosphorylated tau levels) and biochemical (e.g., Cytokines) (Furney et al. 2011) and neuroimaging (e.g., hippocampal and medial temporal lobe atrophy, Pittsburgh compound B (PiB), to identify brain amyloid) (Furney et al. 2011) variables. However, while discrimination, sensitivity and specificity are generally found to improve when utilizing a combination of markers, the samples are usually highly selected and small. Therefore whether these findings can be extrapolated to population screening programs is no known. Further, no cost-effectiveness analysis of adding expensive biological and neuroimaging makers to a MCI diagnosis has yet been undertaken. Other studies have investigated variables linked to an increased risk of dementia in MCI cases and include, for example, non-APOE genetic risk scores (Rodriguez-Rodriguez et al. 2013), health variables (Solfrizzi et al. 2004, Siuda et al. 2009, Stephan et al. 2011) and cognitive and neurological disorders (Anstey et al. 2013a). However, whether these improve risk prediction measures (e.g., discrimination, sensitivity and specificity) over and above the diagnosis of MCI itself, in clinical and/or population-based samples requires testing.

Being able to distinguish those individuals with cognitive decline, including MCI and its associated states, who are at high risk of progressing to dementia from those who are not is important for informing patients/families of outcomes (e.g., allowing for preparation for impending impairment), facilitating targeted intervention (where available) and also for the development of recruitment strategies for MCI clinical trials. Work is currently underway to develop new criteria for clinical and preclinical dementia states that incorporate both clinical and biological

markers (e.g., abnormal cognitive and clinical function combined with CSF/neuroimaging (e.g., positron emission tomography: PET) measures of amyloid-beta accumulation, synaptic dysfunction ([18 F]-fluorodeoxyglucose (FDG) positron emission tomography: FDG-PET/functional magnetic resonance imaging: fMRI), brain structural abnormalities (volumetric magnetic resonance imaging: MRI) and abnormal tau accumulation (in the CSF)). The aim is to improve risk assessment and diagnostic accuracy, with a focus on detecting disease as early as possible (Jack et al. 2010, Sperling et al. 2011).

10.5 Dementia Risk Prediction Models Applicable to the Whole Population

Screening for individuals at risk of dementia is not routinely undertaken in clinical practice and population screening is not currently recommended. However, development of an accurate and validated dementia risk screening tool could be useful for classifying individuals into different groups to inform decision-making. For example, based on the outcome of screening individuals could be classified into: (1) those at high risk who could be referred to specialist services (e.g., a memory clinic) or undergo risk factor treatment or management; (2) those at moderate risk in whom immediate action is not required but rather timed re-screening or a period of watchful waiting may be more appropriate; and, (3) those at low risk who can be excluded from immediate follow-up. However, in order to undertake screening, a method for generating a risk result that is accurate, valid, easy to deliver (e.g., simple and practical), cost-effective and acceptable (e.g., to providers and consumers) is needed. In addition, mechanisms must be in place to deal with the outcomes of screening (e.g., a positive screen result).

Numerous risk factors for cognitive decline and dementia have been identified including for example: demographic (e.g., age, sex, education), socio-economic (e.g., income), lifestyle (e.g., diet, physical and leisure activities, smoking and alcohol consumption), genetic (e.g., APOE, CR1, CLU, BIN1, MS4A, CD2AP, CD33, EPHA1, SORL1 and TREM2), health (e.g., mid-life obesity, hypertension, cerebrovascular disease), psychiatric (e.g., depression) and cognitive variables (e.g., cognitive inactivity, memory impairment and global cognitive decline). Using multivariable analyses both simple and complex models incorporating combinations of these different risk factors have been developed for predicting incident dementia and AD (Stephan et al. 2010a). Table 10.2 gives an overview of the different dementia risk prediction models that have been developed within population-based samples.

As shown in Table 10.2, risk models vary with regard to the type of risk variables incorporated into their calculation (e.g., cognitive, demographic, health, genetic, imaging), the number of risk variables required (range 1 to >20 variables), measurement time (midlife vs. later-life), time frame for prediction (range 2 to >20 years) and the predicted outcome (all-cause dementia vs. AD). Overall, models can be

Table 10.2 Predictors incorporated into dementia and AD risk prediction models in community/population-based samples

Reference	Outcome(s) tested	Range follow-up times	Stage of life at screening	Examples of predictors incorporated into the different models	Range: AUC/c-statistic
Neuropsychological/cognitive					
Hensel et al. (2007)	Dementia and AD	2.5 to 5+ years	Older age	*Neuropsychological* 3-word delayed recall, activity recall task, CASI (Abstraction and Judgment), Digit Letter Test, DSST, episodic memory/recall (free recall rapid/slowly presented random words, free/cued recall organisable words), FOME (recall test), Identical Pictures, IDSR-7, Memory for Text, MMSE, Paired Associates, SIDAM, SRT (delayed recall), TMT-B, verbal fluency (groceries, fruits, flowers, vegetables, animals), visuospatial performance (block design, clock setting, clock reading)	0.59–0.88
Hensel et al. (2009) Jungwirth et al. (2009b) Masur et al. (1994) Nakata et al. (2009) Palmer et al. (2003) Rapp and Reischies (2005)				*Complaint(s)* SMC	

(continued)

Table 10.2 (continued)

Reference	Outcome(s) tested	Range follow-up times	Stage of life at screening	Examples of predictors incorporated into the different models	Range: AUC/c-statistic
Demographic/neuropsychological (with and without cognitive complaints)					
Chary et al. (2013) Hogan and Ebly (2000) Jorm et al. (2005) Nielsen et al. (1999) Tierney et al. (2005) Tierney et al. (2010)	Dementia and AD (probable and possible)	2 to 10 years	Older age	*Demographic* Age, education, sex *Neuropsychological* 3MS, Benton Visual Retention Test, CAMCOG (Memory, General Knowledge and Attention subtests), CASI (Episodic Memory and Visual Construction), DSST, Information Subtest (WMS), IST, MMSE, RAVLT (short delayed recall) and verbal fluency (animals) *Complaint(s)* Memory problem (informant), SMC (CASI Item), SMC (new information)	0.71–0.85
Multivariable models					
Anstey et al. (2013) Barnes and Yaffe (2009)	Dementia and AD	1 to 20+ years	Life-course, mid-life, older age	*Demographic* Age, education, ethnicity, sex *Neuropsychological* 3-word delayed recall, 3MS, Boston (Naming and Similarities subtests), clock drawing, copied drawings (cube, coils, interlocking infinity loops), DSST, figure copying (interlocking pentagons), FCSRT (free recall), memory test (delayed recognition memory of 6 incongruently-coloured objects), MMSE, paper folding, Reid Memory Test, TMT-A, verbal fluency (animals, letters: F, A, S), Verbal IQ (WAIS-R), Word-List Delayed Recall (CERAD)	0.66–0.91
Barnes et al. (2010)				*Complaint* Memory problem (informant), proxy (IQCODE), self-report attention difficulties, severe memory loss (self or informant), SMD, SMI (with and without worry)	

(Brandt and Rogerson (2011), Brandt et al. (2013))	*Health* AF, angina, anxiety, aortic calcification, arthritis, blood glucose level, blood pressure (systolic and diastolic), BMI, brain disorders (tumour, any surgery, any other brain disorder), bypass surgery, calf pain, carotid artery thickening, chest pain (excited and when walking up hill), cholesterol (total, HDL-C), chronic heart failure, COPD, claudication, defective ventricular conduction, depression (CES-D), diabetes, dizziness, encephalitis, epilepsy, first and second heart sound abnormal, HbA1c, heart disease, Huntington's disease, hypercholesterolemia, hypertension (including treatment), multiple sclerosis, myocardial infarction, normal pressure hydrocephalus, PAD, PD, pulmonary congestion, sinus tachycardia, ST depression, stroke, systolic murmur, TIA, traumatic brain injury, T-wave abnormalities, waist-to-hip ratio
Chary et al. (2013)	*Genetics* APOE, genetic risk score (including CLU, PICALM, BIN1, CR1, ABCA7, MS4A6A, MS4A4E, CD2AP, EPHA1, CD33)
Exalto et al. (2013)	*Physical function* IADLs, speed (buttoning)
Hogan and Ebly (2000)	*Lifestyle* Alcohol intake, cognitive activity, diet (fish intake), physical activity, smoking, social engagement

(continued)

Table 10.2 (continued)

Reference	Outcome(s) tested	Range follow-up times	Stage of life at screening	Examples of predictors incorporated into the different models	Range: AUC/c-statistic
Holtzer et al. (2008) Jessen et al. (2011) Jungwirth et al. (2009a) Kivipelto et al. (2006) Mitnitski et al. (2006) Ohara et al. (2011) (Reitz et al. (2010)) Seshadri et al. (2010) Verhaaren et al. (2013) Waite et al. (2001)				*Other* Brain MRI (white matter disease and enlarged ventricles), extrapyramidal score (measures of tone, bradykinesia, resting tremor, postural flexion, glabella tap), extrapyramidal gait disorder (5 m timed walk), family history (dementia), pesticide exposure, within persons across test variability (on cognitive measures)	

Updated and adapted from: Stephan et al. (2010)

3MS Modified Mini Mental State, *AF* atrial fibrillation, *AUC* area under the curve, *BMI* body mass index, *c-statistic* concordance statistic, *CAMCOG* Cambridge Cognitive Examination, *CASI* cognitive abilities screening instrument, *CERAD* Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery, *CES-D* Center for Epidemiologic Studies Depression Scale, *COPD* chronic obstructive pulmonary disease, *DSST* Digit Symbol Substitution Test, *FCSRT* Free and Cued Selective Reminding Test, *FOME* fuld object memory evaluation, *HDL-C* high density lipoprotein cholesterol, *IADLs* instrumental activities of daily living, *IDSR-7* Intra-Categorical Delayed Selective Reminding Test, *IQCODE* informant questionnaire on cognitive decline in the elderly, *IST* Isaacs Set Test, *MMSE* Mini Mental State Examination, *MRI* magnetic resonance imaging, *PAD* peripheral artery disease, *PD* Parkinson's disease, *RAVLT* Rey Auditory Verbal Learning Test, *SIDAM* structured interview for the diagnosis of dementia of the Alzheimer type, *SMC* subjective memory complaint, *SMD* subjective memory decline, *SMI* subjective memory impairment, *SRT* Buschke Selective Reminding Test, *TIA* transient ischemic attack, *TMT-A* Trail Making Test Part A, *TMT-B* Trail Making Test Part B, *WAIS* Wechsler Adult Intelligence Scale, *WAIS-R* Wechsler Adult Intelligence Scale-Revised, *WMS* Wechsler Memory Scale

broadly divided into three categories: (1) neuropsychological based models (incorporating cognitive test scores, with or without subjective memory/cognitive complaints and demographic information such as age and educational attainment); (2) health-based models (incorporating self-reported or objectively measured health status including measures of cardio-metabolic and neurological health); and (3) multifactorial models (typically combining demographic and cognitive measures with health status or genetic variables). Generally, model accuracy ranges from low (e.g., AUC = 0.59) to moderate (AUC = 0.88), with only one model being classified as excellent (i.e., AUC = 0.91) (Jungwirth et al. 2009a).

As concluded by the review (Stephan et al. 2010a), no model at present can be recommended for use within a population-screening program. None have been externally validated and therefore transportability of models to populations outside those from which they were derived is not known. However, validation of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score has been attempted, although not all variables were available in the validation dataset (Exalto et al. 2013). Further, no cost-effectiveness analysis regarding the calculation or implementation of dementia risk screening using any model has been undertaken in clinical or population-based samples. The harms associated with screening in otherwise healthy populations have not been determined (e.g., stigma and anxiety associated with being labelled at high risk of dementia) nor are there treatment options available.

However, being able to screen for risk of dementia would have a number of benefits as it could: (1) allow for targeted risk factor reduction to an individual's unique combination of risk and protective factors and therefore allow for personalized intervention; (2) provide a standardized method to enrol those individuals who are mostly likely to benefit from intervention into clinical trials; (3) give high-risk individuals and their families time to prepare for future disease and reduce worry in low-risk individuals; and (4) be used as the basis for population health policy, for example, to provide government with estimates of future burden of disease and associated resource implications (e.g., on the health care system) allowing for better advanced planning.

10.6 Limitations of Current Dementia Risk Prediction Methods

There are a number of limitations to current dementia risk prediction methods as outlined below:

- *Age*: Models have generally not been built stratified by age. This is problematic as associations between risk variables (particularly vascular related risks such as obesity and hypertension) have not been consistently observed across different age groups (e.g., mid-life vs. young–old vs. very old).
- *Ethnic diversity*: Most models have been built in Caucasian populations and have not been externally validated across geographical borders or in different ethnic groups.

- *Feasibility and risk-benefit*: It is not known whether screening for dementia risk leads to improved patient outcomes, what are the harms of screening for dementia risk or whether screening is feasible in currently constrained consultation times with restricted budgets for measuring risk variables and attaining the risk score (e.g., direct and indirect costs). Further are practical issues such as who will collect the risk factor data, calculate the risk score (e.g., nurse, general practitioner (GP), psychiatrist) and who will be responsible for referral, intervention planning and patient follow-up.
- *Ethical and legal issues*: Currently there is no treatment to reverse the pathological changes associated with dementia. Without an effective treatment and only modest improvement seen with currently available early treatments, questions are raised about the need to screen for dementia risk in otherwise healthy individuals. Further, the lack of a risk model with high accuracy and sensitivity/specificity warrants caution in the use of current tools (in either clinical or population-based samples) and if such tools are used how risk scores are utilized given their low to moderate accuracy. Also, any risk prediction program must not lead to inequality and must be equally accessible.
- *Attitudes to screening*: Academic, clinical and public attitudes to dementia risk screening have not been studied in enough detail to determine acceptance.

10.7 Cardiovascular Disease Risk Assessment Tools and Cognitive Function

Cardio-metabolic diseases in mid-life (e.g., hypertension, diabetes) and their risk factors (e.g., smoking, high alcohol consumption, low levels of physical activity) have been associated with chronic brain perfusion, AD and vascular neuropathology, and have been linked to an increased risk of later life cognitive decline and dementia (de la Torre 2010, Richardson et al. 2012). Given this link, several studies have tested whether models developed for the prediction of cardiovascular disease in clinical settings are also associated with cognitive function. The most widely applied models are the Framingham Risk Scores (FRS) for predicting 10-year incident stroke (incorporating: age, systolic blood pressure, diabetes, smoking, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy and use of hypertensive medication) (D'Agostino et al. 1994), coronary heart disease (CHD) (incorporating: age, low and high density lipoprotein (LDL and HDL) cholesterol, systolic and diastolic blood pressures, diabetes and current smoking) and general cardiovascular disease that combines coronary heart disease, cerebrovascular disease, peripheral arterial disease and heart failure (incorporating: age, treated and untreated systolic blood pressure, diabetes, smoking, total and HDL cholesterol and the body mass index (BMI) replacing lipids in a simpler model) (D'Agostino et al. 2008). Findings of the association between each of the different vascular risk scores and cognitive function in cohort studies with longitudinal designs are outlined below.

10.7.1 Framingham Stroke Risk (FSR) Score

Using data from the Normative Aging Study (USA), the FSR score was found to be inversely associated with verbal fluency, but not word list recall, digit span or pattern comparison over 3 years of follow-up in men (Brady et al. 2001). In another USA-based study (The Reasons for Geographical and Racial Difference in Stroke: (REGARDS) study), the FSR score was found to be associated with global cognition measured using a Six Item Screener (SIS) test incorporating a 3-item recall question and three orientation items (to year, day and month), over an average follow-up of 4 years (up to 6 years) (Unverzagt et al. 2011). Data from the English Longitudinal Study of Ageing (ELSA), also found that the FSR score (excluding left ventricular hypertrophy) was significantly associated with global cognitive function (Mini Mental State Examination: MMSE score), in addition to memory and executive performance over 4 years of follow-up (Dregan et al. 2013). Findings from the Whitehall II Study (UK), suggest that over a longer follow-up period (i.e., 10 years) the FSR score is associated with decline in reasoning, fluency (phonic and semantic), vocabulary and global cognitive function, but not memory performance (Kaffashian et al. 2013).

Overall, the results suggest that the FSR score is associated with global cognitive decline and impairment in non-memory cognitive domains over both short- and long-term follow-up periods. The observed associations may be linked to a decrease in brain volume that has been shown in individuals with high FSR scores (Seshadri et al. 2004).

10.7.2 Framingham General CVD Risk Score

Findings from the English Longitudinal Study of Ageing (ELSA) suggest that the FRS for general CVD is associated with global cognitive function, memory and executive performance over 4 years of follow-up (Dregan et al. 2013). In the Whitehall II Study, over a longer follow-up period (10 years), higher general CVD risk was found to be associated with decline in reasoning, fluency (phonemic and semantic), vocabulary and global cognition, but not memory (Kaffashian et al. 2013). Where analyses have been stratified by gender, higher CVD risk scores were significantly associated with poor reasoning over time in men (Kaffashian et al. 2011).

10.7.3 Framingham Coronary Heart Disease Risk Score

Results from the Rancho Bernardo Study (USA) found that the FRS for predicting CHD was associated with more rapid decline in memory and verbal fluency early in follow-up and with longitudinal trajectory of global cognitive functioning (MMSE score) and executive performance (Trail Making Test), in women but not in men (Laughlin et al. 2011). The follow-up period was 10 years.

10.7.4 Non-Framingham Vascular Risk Scores

The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study score is a dementia-specific risk prediction model that incorporates age, education, sex, genetics (APOE e4 status, extended model only) and mid-life health (including: systolic blood pressure, BMI, total cholesterol and physical activity). This score has been found to be associated with an increased risk of incident dementia over 20 years of follow-up (Kivipelto et al. 2006). Using data from the Hoorn Study (The Netherlands), over 15 years of follow-up, the CAIDE dementia risk score was found to be associated with impairments in information processing speed (AUC = 0.63; 95%CI: 0.53–0.73) and abstract reasoning (AUC = 0.72; 95%CI: 0.61–0.82), but not memory (working and delayed), attention and executive function, information processing speed or language (Reijmer et al. 2011). Visuoconstruction performance was also significantly associated with the CAIDE risk score; however, prognostic performance was not reported. The CAIDE risk score had moderate sensitivity for information processing speed and abstract reasoning (71 % and 77 %, respectively), but low specificity (44 % and 46 %, respectively). Results from the Whitehall II Study found that over 10 years the CAIDE score was associated with reasoning, vocabulary and global cognition, but not memory or fluency (phonemic or semantic) (Kaffashian et al. 2013). This study compared the CAIDE and FRS (for stroke and general CVD) and found that the Framingham scores showed stronger associations with cognitive decline when compared to the CAIDE risk score. The authors concluded that the Framingham scores might be more suited to predicting non-dementia cognitive outcomes. Further comparison of different risk scores across different studies and populations is needed to replicate these results.

10.7.5 Summary

Taken together, the results suggest that a combination of vascular disease and its risk factors is associated with cognitive decline (usually in global cognitive function and non-memory domains). Therefore, treatment and prevention strategies should look at multiple underlying, and potentially modifiable causes to an individual's cognitive impairment.

10.8 Cost Implications: Attaining the Risk Score

No study has compared the estimated cost of attaining each of the different risk scores. Indeed, the use of risk scores based on complex biomarkers (e.g., genetics and neuroimaging) require technologically advanced, costly, and not easily available methods in most clinical and research settings. Further, increased costs, limited accessibility to necessary model components and requirements for high expertise may offset any advantage of more advanced models.

One study has however considered the impact on discriminative accuracy of modifying the calculation of a resource-intensive risk score to incorporate less expensive measures. The original model, the Late Life Dementia Risk Index, included demographic, lifestyle, neuropsychological, medical, physical functioning, genetic, cerebral magnetic resonance imaging (MRI) and carotid artery ultrasound measures, and had moderate accuracy for the prediction of 6-year incident dementia (c-statistic = 0.81) (Barnes et al. 2009). The revised model included demographic, lifestyle, neuropsychological and medical factors, and while having significantly lower accuracy (c-statistic = 0.77), was able to categorize subjects as having low, moderate or high risk of dementia with similar accuracy to the more complex score (Barnes et al. 2010). In another study, a risk model has been developed using only self-reported risk factors (Anstey et al. 2013b) and in a further study a score has been developed for easy application through the Internet (Brandt and Rogerson 2011, Brandt et al. 2013). This has important implications for possibly simplifying risk prediction (e.g., removing the need for specialist equipment or training necessary for example, for administering neuropsychological batteries and collecting health variables such as blood pressure to assess hypertension or blood for determining cholesterol levels) and reducing costs particularly important if assessing risk at a population level. However, the predictive accuracy of these models has not yet been tested.

Estimating dementia risk based on cardiovascular screening models (e.g., such as the Framingham Risk Scores), could be more applicable in primary care settings as typically, in most countries (Western), data on cardiovascular disease and its risk factors are routinely collected during clinical consultations. However, while the FRS for stroke, CVD and CHD have been found to be associated with cognitive function in some studies results have not been consistent. Further, whether these scores are predictive of dementia has not yet been tested, with the focus of research to date on predicting changes in global and domain specific (e.g., memory and attention) cognitive functioning.

10.9 Conclusion

Within the field of dementia a key research priority is the development of a tool for early identification of individuals at high risk of dementia over short- and long-term follow-up and in different age groups. This has implications for improving diagnostics and undertaking of more targeted risk factor reduction in older aged populations. Indeed, having a dementia risk model could form part of a personalized medicine plan whereby for each individual their unique risk profile could be identified and the components that are largely contributing to their risk score targeted with available interventions. Knowing the profile of high-risk cases and the proportion of the population likely to fall into the high-risk category will also be important for budgeting decisions regarding future care and service needs of the older population. While several dementia risk models have been developed in population-based

samples less that 1 % have been externally validated. This raises questions of validity of the models and generalisability to other populations with different ethnic and sociodemographic characteristics. More work needs to be done on validating current risk models and testing the contribution of the different risk variables to determine the most parsimonious risk score without compromising accuracy. Being able to screen for risk of dementia could have a number of benefits including: better targeting of clinical trials, opportunities for advanced planning before disease onset, prioritization of treatment, where available, and could better inform government policy in terms of future health care needs and resource allocation.

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Chapter 11
Lifestyle Factors in the Prevention of Dementia: A Life Course Perspective

Chengxuan Qiu

11.1 Introduction

Dementia is a clinical syndrome characterized by progressive deterioration in memory and other cognitive domains. Dementia is a major cause of functional dependence, institutionalization, poor quality of life, and mortality in older people. According to the World Alzheimer Report of Alzheimer's Disease International, in 2010 the total worldwide number of people with dementia was estimated at about 36 million; the total costs of dementia, including direct cost of medical care, cost of informal care provided by family and others, and cost of social care provided by community care professionals, exceeded US$600 billion (Wimo et al. 2013; Prince et al. 2013). It was projected that 115 million people worldwide would live with dementia by 2050, with a markedly increasing proportion of patients living in low- and middle-income countries (Wimo et al. 2013). The worldwide current burden and future projection of number of people with dementia might well have been underestimated given the fact that recent reports have shown that the burden of dementia in China and other middle-income countries may increase faster than is generally assumed by the international health community (Prince et al. 2012; Chan et al. 2013).

Clinically, Alzheimer's disease is the most common form of dementia which accounts for up to 70 %, followed by vascular dementia which accounts for 20–25 %, of all dementia cases (Reitz et al. 2011; Fratiglioni and Qiu 2013). However, population-based postmortem and neuroimaging studies have revealed that the neuropathological spectrum of clinical dementia ranges from predominantly cerebrovascular lesions (e.g., infarcts and microvascular lesions) to primarily neurodegenerative pathologies (i.e., amyloid plaques and neurofibrillary tangles): there are few cases with relatively pure vascular dementia on one end, few with relatively

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pure Alzheimer dementia on the other end, and in between the large majority of patients with mixed cerebrovascular and degenerative pathologies (Schneider et al. 2007; Viswanathan et al. 2009; Wharton et al. 2011). Although the etiology of dementia is not fully understood, it is well known that dementia is a multifactorial disorder and that the risk of late-life dementia is likely to be determined by interplay between genetic susceptibility and environmental factors over the lifespan. Of those modifiable factors, lifestyle behavioral factors (e.g., cigarette smoking, excessive alcohol consumption, and physical inactivity) and cardiometabolic risk factors (e.g., obesity, hypertension, hyperlipidemia, and diabetes) have been increasingly recognized as potential etiological factors for dementia including Alzheimer dementia (Barnes and Yaffe 2011; Qiu 2012). In this chapter, I briefly review population-based epidemiological studies that investigate lifestyle and metabolic factors for dementia as well as neuroimaging and neuropathological studies that explore the potential pathological mechanisms linking lifestyle and metabolic-related factors to dementia, aiming, from a life course perspective, to propose possible intervention strategies against dementia. Special attention is paid to the most recent studies and, whenever available, to systematic reviews and meta-analyses of population-based prospective studies and preventative controlled trials.

11.2 Epidemiological Evidence

In the last two decades, lifestyle and cardiometabolic risk factors for dementia have been the major focus of numerous epidemiological studies in the world. The associations of dementia with almost all these factors have been assessed in systematic reviews and quantitative meta-analyses of population-based prospective studies, as summarized in Table 11.1.

11.2.1 Lifestyle and Health Behavioral Factors

Cigarette smoking. Numerous prospective studies have shown that smoking, even secondhand smoking, is associated with an increased risk of dementia syndrome (Barnes and Yaffe 2011; Qiu 2012; Chen 2012). In addition, midlife heavy smoking ($\geq$2 packs per day) is associated with a double risk for dementia (Rusanen et al. 2011), although the association might be attenuated by selective survival bias owing to smoking. The meta-analyses of follow-up studies indicate that current smoking, as compared with never smoking, is associated with around 50–60 % increased risk for dementia (Anstey et al. 2007; Peters et al. 2008c; Cataldo et al. 2010). Furthermore, the systematic reviews reveal that the impact of smoking on dementia may vary by age, such that smoking is more harmful for younger than older ages. Thus, population-based prospective studies have provided rather convincing evidence suggesting that smoking is a risk factor for dementia including Alzheimer dementia.

Table 11.1 Lifestyle factors over the lifespan in dementia: summary of systematic reviews and meta-analyses of prospective studies

Lifestyle factors	Study description	Pooled relative risk (95 % CI) and conclusions
Smoking		
Anstey et al. (2007)	Meta-analysis of 19 cohort studies	1.3 (1.0–1.6). Elderly smokers have an increased risk for dementia
Peters et al. (2008c)	Meta-analysis of eight cohort studies, age ≥65 years	1.6 (1.2–2.2). Current smoking increases risk of Alzheimer's disease among older people (≥65 years)
Cataldo et al. (2010)	Meta-analysis of 14 cohort studies with no affiliation of tobacco industry	1.5 (1.2–1.8). Current smoking is a risk factor for Alzheimer's disease
Alcohol consumption		
Peters et al. (2008a, b, c)	Meta-analysis of 23 cohort studies, age ≥65 years	0.6 (0.5–0.8). Limited alcohol intake in early adult life may protect against dementia
Anstey et al. (2009)	Meta-analysis of 15 cohort studies	0.7 (0.6–0.9). Late-life alcohol consumption is associated with a reduced risk of dementia
Physical activity		
Hamer and Chida (2009)	Meta-analysis of 16 cohort studies	0.7 (0.6–0.9). Physical activity is inversely associated with the risk of dementia
Morgan et al. (2012)	Meta-analysis of 18 cohort studies	0.8 (0.7–0.9). Physical activity is inversely associated with the risk of dementia
Blood pressure		
Qiu et al. (2005)	Systematic review of population studies and major clinical trials	High blood pressure in midlife, not in late life, is associated with increased risk of dementia. There is an age-dependent association between level of blood pressure and risk of dementia
Barnes and Yaffe (2011)	Meta-analysis of five cohort studies	Midlife hypertension: 1.6 (1.2–2.2). Hypertension in midlife increases risk of Alzheimer's disease
Power et al. (2011)	Systematic review and meta-analysis of 18 cohort studies	Hypertension: 1.0 (0.8–1.2). The association of Alzheimer's disease with hypertension depends on age

(continued)

Table 11.1 (continued)

Lifestyle factors	Study description	Pooled relative risk (95 % CI) and conclusions
Obesity		
Beydoun et al. (2008)	Meta-analysis of ten cohort studies, age 40–80 years	Overall, 1.4 (0.9–2.2); age <60 years, 1.7 (1.3–2.3); age ≥60, 1.3 (0.7–2.4). Obesity in middle age is associated with increased risk of dementia
Profenno et al. (2010)	Meta-analysis of eight cohort studies	1.6 (1.0–2.5). Obesity is associated with increased risk of Alzheimer's disease
Anstey et al. (2011)	Meta-analysis of 15 prospective studies	Midlife overweight 1.3 (1.1–1.4); midlife obesity 1.6 (1.3–2.0). Midlife overweight and obesity increase risk of dementia
Loef and Walach (2013)	Meta-analysis of 13 cohort studies	Midlife (40–59 years) overweight 1.3 (1.1–1.7); midlife obesity 1.9 (1.4–2.6); late-life (≥60 years) overweight or obesity 0.8 (0.7–0.9). Midlife obesity increases risk of late-life dementia
Total cholesterol		
Anstey et al. (2008)	Systematic review of 18 cohort studies; four studies had data on midlife cholesterol	Midlife high cholesterol increases dementia risk; there is no association of late-life total cholesterol with dementia
Shepardson et al. (2011)	Systematic review of all well-controlled studies	Alzheimer's disease had negative association with late-life high cholesterol but had a positive association with midlife high cholesterol
Diabetes		
Profenno et al. (2010)	Meta-analysis of nine prospective studies	1.5 (1.3–1.8). Diabetes increases Alzheimer's risk independent of vascular morbidities
Kopf and Frölich (2009)	Systematic review of 11 cohort studies	Diabetes increases risk of Alzheimer's disease
Lu et al. (2009)	Meta-analysis of eight prospective studies	1.5 (1.3–1.7). Diabetes increases dementia risk independent of vascular comorbidities
Cheng et al. (2012)	Meta-analysis of 19 prospective studies	1.5 (1.3–1.7). Diabetes is associated with increased risk of dementia
Vagelatos and Eslick (2013)	Meta-analysis of 16 prospective studies	1.6 (1.4–1.8). Diabetes increases Alzheimer's risk independent of vascular comorbidities

Alcohol consumption. Long-term excessive consumption of alcohol causes alcoholic dementia. By contrast, follow-up studies of older people often reported a reduced incidence of dementia associated with light-to-moderate alcohol intake, suggesting that limited alcohol consumption may protect against dementia (Qiu 2012). This has been confirmed by systematic reviews and meta-analyses of prospective studies, which show that light-to-moderate alcohol intake reduces dementia risk by 30–40 % (Peters et al. 2008b; Anstey et al. 2009). However, the apparent beneficial effects of limited alcohol intake in reducing risk of dementia are likely owing to potential biases such as information bias, confounding of lifestyle factors and socioeconomic status, and inconsistent approaches of quantitative alcohol assessment across studies.

Physical (in)activity. US studies of older people suggested that total daily physical activity (exercise or non-exercise) or vigorous physical activity (e.g., aerobics, sports, and running) may reduce risk of dementia (Buchman et al. 2012; Bowen 2012). In addition, weekly-to-daily regular physical exercise, even low-intensity exercise such as walking, may reduce dementia risk and benefit cognitive function (Qiu 2012). Such an effect was reinforced by a follow-up study that showed a possible dose–response association between an increasing level of physical activity and a gradual reduction in dementia risk (Scarmeas et al. 2009). The meta-analyses of prospective studies yielded an approximately 20–30 % decreased risk of dementia in the highest, as compared with the lowest, group of leisure-time physical activity (Hamer and Chida 2009; Morgan et al. 2012).

11.2.2 Cardiometabolic Risk Factors

High blood pressure and use of antihypertensive agents. Long-term observational studies often suggest that midlife high blood pressure is associated with an increased risk of dementia later in life (Qiu et al. 2010b). Pooled analysis suggested that midlife hypertension was associated with a 60 % increased risk of late-life Alzheimer dementia (Barnes and Yaffe 2011). Thus, it has been proposed that control of midlife high blood pressure can be an effective strategy to reduce the risk of late-life dementia (Launer et al. 2010). By contrast, the follow-up studies of older adults (e.g., age ≥65 years) often found no, or an inverse, association between level of blood pressure and risk of dementia; this has been interpreted as a consequence of the disease process because dementia usually has a long latent period and blood pressure may be lowered during the preclinical phase of dementia caused by degeneration of neurons that regulate blood pressure (Qiu et al. 2005). Thus, systematic reviews of observational studies from a life course perspective appear to support an age-varying association of blood pressure with risk of dementia, although their causal relationship remains to be established (Power et al. 2011). In fact, the lack of association between levels of blood pressure and risk of dementia can be concluded in systematic reviews when blood pressures at middle age and late life are not separately assessed (Guan et al. 2011; Power et al. 2011).

Use of antihypertensive drugs has frequently been linked to a reduced incidence of dementia in numerous population-based observational studies as summarized in systematic reviews (Qiu et al. 2005; Duron and Hanon 2010; Levi Marpillat et al. 2013). The beneficial effect may depend on the type of drugs, clinical features of patients, as well as age and duration of therapy, such that the protective effect is more evident for middle-aged or young-old people, for calcium-channel blockers or angiotensin receptor blockers, for patients with a history of cerebrovascular disease, and for relatively long-term use (Haag et al. 2009; Li et al. 2010; Yasar et al. 2013; Gelber et al. 2013).

However, among the major clinical trials that tested the effect of different antihypertensive agents in reducing risk of dementia, only the Syst-Eur Trial showed clear evidence of a protective effect of calcium-channel blockers against dementia. The PROGRESS trial of patients with a history of cerebrovascular disease showed that antihypertensive therapy might reduce the risk of dementia and cognitive decline related to recurrent stroke. The HYVET-COG of people aged ≥80 years found a nonsignificant reduction in dementia risk related to antihypertensive therapy (Peters et al. 2008a). The Cochrane review of the major randomized clinical trials found no convincing evidence that blood pressure-lowering therapy could prevent dementia (McGuinness et al. 2009b). The meta-analyses of clinical trials also found no evidence that antihypertensive therapy reduced the risk of dementia (Staessen et al. 2011; Levi Marpillat et al. 2013). The negative results from most clinical trials are likely due to the fact that all these trials were conducted among older people (e.g., age >60 or 65 years) when high blood pressure was no longer acting as a risk factor for dementia (Qiu 2012).

Obesity or overweight. Long-term follow-up studies suggested that midlife overweight or obesity was associated with an increased risk of dementia later in life, whereas body mass index (BMI) in late life (≥65 years) was inversely related to dementia risk (Beydoun et al. 2008; Fitzpatrick et al. 2009; for a more detailed discussion of this shift in association, see Dahl Aslan 2014). These studies also revealed a gradual decline in BMI over the years prior to dementia onset, which is in line with the finding of association between low BMI and increased risk of dementia from short-term follow-up studies in older people. The meta-analyses of cohort studies suggested a 40–60 % increased risk of dementia associated with obesity; such an association was stronger in studies with a longer follow-up period (>10 years) and with obesity measured at a younger age (Profenno et al. 2010; Anstey et al. 2011; Loef and Walach 2013). Thus, the lifespan-dependent association of BMI with risk of dementia has emerged, such that midlife obesity is a risk factor for dementia, whereas low BMI in late life and weight loss after middle age can be markers of prodromal dementia.

High cholesterol and use of statins. Similar to blood pressure and BMI, prospective studies also support an age-dependent association of total cholesterol with risk of dementia, such that high cholesterol at midlife is associated with an increased risk of dementia, whereas no, or an inverse, association between late-life total cholesterol and risk of dementia is often observed. The age-varying association was also

concluded by the systematic reviews and meta-analyses (Anstey et al. 2008; Shepardson et al. 2011). Long-term follow-up studies also reveal that total serum cholesterol level begins to decline over a decade before dementia onset, suggesting that decline in total cholesterol after midlife and low cholesterol in late life may be markers for prodromal dementia (Qiu 2012).

The association of high cholesterol with increased risk of dementia implies that cholesterol-modifying therapy may help prevent the disease. Indeed, cross-sectional studies often suggest a decreased likelihood of dementia associated with use of cholesterol-lowering drugs (statins) (Qiu 2011, 2012). However, follow-up studies of older adults found no clear beneficial effect of statin therapy against dementia (Ancelin et al. 2012). The meta-analysis of follow-up studies revealed a slightly beneficial effect in the prevention of dementia associated with statin therapy, but the effect was likely due to biases (e.g., information bias, confounding, and selection bias) common in observational studies (Wong et al. 2013).

Despite biological plausibility of increased cholesterol being involved in neurodegeneration, large-scale randomized controlled trials of individuals with high total cholesterol fail to demonstrate any benefits of statin therapy in maintaining cognitive function and in reducing risk of dementia (McGuinness et al. 2009a). In addition, two major randomized clinical trials found that cholesterol-lowering therapy with atorvastatin or simvastatin in patients with mild-to-moderate Alzheimer dementia had no cognitive benefits (Feldman et al. 2010; Sano et al. 2011). The clinical efficacy of statins in the treatment of dementia is not supported by current evidence from a Cochrane review (McGuinness et al. 2013). Taken together, evidence from randomized clinical trials of statin therapy has so far consistently shown no preventative or therapeutic effect on dementia and Alzheimer's disease.

Diabetes. The association of diabetes with increased risk of dementia is supported by systematic reviews and quantitative meta-analyses of follow-up studies, in which diabetes increases the risk of dementia by approximately 50 % independent of vascular comorbidities (Kopf and Frölich 2009; Lu et al. 2009). Recent studies added further support to the association (Mayeda et al. 2013; Tolppanen et al. 2013). In addition, several studies have suggested that among older adults with diabetes, there appears to be an association of hypoglycemic episodes or hypoglycemia with increased risk of dementia (Whitmer et al. 2009; Lin and Sheu 2013; Yaffe et al. 2013), although a higher blood glucose level might also be related to an increased risk of dementia (Crane et al. 2013; Yaffe et al. 2013; see also Herghelegiu and Prada 2014). Finally, long-term follow-up studies show that midlife-onset diabetes, as compared to late-life diabetes, is more strongly associated with an elevated risk of dementia (Xu et al. 2009; Tolppanen et al. 2013), suggesting that long-term and more severe diabetes may play a crucial role in dementia.

Aggregation of lifestyle and metabolic risk factors. The metabolic syndrome (MetS), as a cluster of multiple interrelated metabolic risk factors, has been frequently linked to vascular dementia and dementia in general. Indeed, the traits of MetS (e.g., diabetes, midlife hypertension, and obesity) have been associated with an increased risk of dementia. However, evidence from population-based follow-up studies of

older adults has been mixed in linking MetS to specific Alzheimer dementia (Raffaitin et al. 2009; Forti et al. 2010). It is likely that, owing to pathophysiological changes of metabolic risk factors with age, a cluster of late-life metabolic factors may not be superior to its individual components in defining the risk of degenerative dementia. In addition, lifestyle, cardiovascular risk factors, and related vascular comorbidity often coexist among older people. Recent studies have suggested that having a pattern of healthy lifestyle behaviors (e.g., no smoking, normal weight, physical activity, and healthy diet) in middle age or later in life is associated with a lower risk for dementia (Gelber et al. 2012; Norton et al. 2012). Population-based follow-up studies also have shown that aggregation of cardiovascular risk factors such as smoking, hypertension, diabetes, and hypercholesterolemia at middle age or several years before dementia onset incrementally increases the risk for dementia (Qiu 2012). Risk indices for predicting risk of dementia also have been proposed for middle-aged and elderly people, in which lifestyle and cardiometabolic risk factors constitute the critical part (Barnes et al. 2009; Reitz et al. 2010; Exalto et al. 2013; for a discussion of dementia risk prediction models, see Stephan 2014).

11.3 Biological Plausibility

Postmortem imaging studies have confirmed that regional brain atrophy (e.g., hippocampus and medial temporal lobe) is a reliable marker for local neurodegenerative pathology, whereas white matter hyperintensities, lacunar infarcts, and microbleeds in the brain are markers for cerebrovascular disease. Thus, the high-quality neuroimaging techniques (e.g., MRI, diffusion tense imaging, and positron emission tomography) make it possible now to investigate in vivo the burden of brain pathologies. Studies that integrate pathological and neuroimaging data with comprehensive epidemiological and clinical data provide deep insight into neuropathological mechanisms that link lifestyle and cardiometabolic risk factors to brain pathology and dementia syndrome. Lifestyle and cardiometabolic factors are hypothesized to be involved in the development and clinical expression of dementia syndrome by causing cerebrovascular lesions and possibly by influencing neurodegenerative processes.

11.3.1 Cerebral Macro- and Microvascular Lesions

Smoking, long-term chronic hypertension, and diabetes are major risk factors for cerebral atherosclerotic and arteriosclerotic disorders (e.g., atherosclerosis, brain infarcts, white matter lesions, microinfarcts, and microbleeds). Severe intracranial atherosclerosis and related macro- and microvascular diseases may increase the odds of dementia independent of Alzheimer pathologies through different pathways. First, cerebral atherosclerosis or arteriosclerosis can induce cerebral hypoperfusion, which in turn triggers accelerated deposition of amyloid-β (Aβ) and

contributes to cognitive deterioration and expression of dementia syndrome in the presence of a relatively small burden of neurodegenerative pathologies (Dolan et al. 2010; Strozyk et al. 2010; Garcia-Alloza et al. 2011). Furthermore, cerebral microvascular changes (e.g., microinfarcts, microbleeds, white matter lesions, and loss of white matter integrity) have been increasingly recognized as the potential pathological mechanisms leading to cognitive impairment and dementia (Qiu et al 2010a; Pantoni 2010; Launer et al. 2011; Arvanitakis et al 2011; Smith et al. 2012). This is supported by studies showing that the association of certain cardiovascular risk factors (e.g., hypertension and diabetes) with dementia is largely mediated by mixed cerebrovascular and neurodegenerative pathologies (Reijmer et al. 2013; Vagelatos and Eslick 2013; Qiu et al. 2014). Finally, atherosclerosis and neurodegeneration in the brain share common pathogenic mechanisms, such as oxidative stress, inflammation, and toxic Aβ, in which cerebrovascular and neurodegenerative pathology may represent independent pathological processes that converge to cause additive brain damage and thus to promote manifestation of dementia syndrome (Casserly and Topol 2004).

11.3.2 Cerebral Neurodegenerative Pathology

Population-based postmortem and neuroimaging studies have linked cigarette smoking and hypertension to neuritic plaques, neurofibrillary tangles, and hippocampal atrophy (Qiu 2012; Debette et al. 2011). Physical inactivity and obesity may contribute to global and regional brain atrophy (Hafsteinsdottir et al. 2012). Neuroimaging and autopsy-verified data suggest that diabetes and hyperinsulinemia may accelerate brain atrophy and the formation of neuritic plaques (Matsuzaki et al. 2010; van Elderen et al. 2010), although a review of clinicopathological studies provided no evidence linking diabetes to the burden of amyloid plaques and neurofibrillary tangles (Kalaria 2009). This may imply that less degenerative pathologies are needed in the brain for expression of dementia syndrome among elderly people with diabetes. Finally, neuropathological benefit of antihypertensive therapy is supported by studies showing that use of antihypertensive drugs is associated with less Alzheimer pathologies (Hoffman et al. 2009). Taken together, evidence linking lifestyle and metabolic risk factors to neurodegeneration is less convincing than that for cerebrovascular lesions.

11.3.3 Mixed Cerebrovascular and Neurodegenerative Pathology in Dementia

Clinically silent Alzheimer and cerebrovascular pathologies often coexist among older people, especially among those with unhealthy lifestyle and metabolic risk factors; both pathologies may develop in parallel and are likely to be accelerated

by these unhealthy lifestyle and metabolic factors. Brain vascular lesions act interactively with concomitant neurodegenerative pathologies to produce cognitive dysfunction, where expression of dementia syndrome depends on the relative burden of vascular and neurodegenerative pathologies in the brain; more vascular lesions may disclose expression of dementia syndrome in people with less degenerative pathologies, and vice versa.

11.4 Primary Prevention

Prevention of late-life chronic disorders such as dementia is critical to achieve the European target of a 2-year increase in healthy life years by 2020 (Jagger et al. 2013; Robine et al. 2013). Identifying major modifiable risk factors for dementia provides a great potential for primary prevention of the disease (Barnes and Yaffe 2011; Fratiglioni and Qiu 2013). Indeed, in the last two decades, great progress has been made in understanding the etiological factors and pathological mechanisms for dementia including Alzheimer dementia. As summarized above, current evidence from multidisciplinary research tends to support the notion that, from a life course perspective, preventative strategies aiming at postponing the onset of late-life dementia by targeting lifestyle and major metabolic risk factors are likely to be effective if implemented in middle-aged and older people living in the community (Fratiglioni and Qiu 2013). It has been estimated that delaying the onset of dementia by 5 years would halve the prevalence of dementia and substantially decrease the number of dementia cases in the community; delaying the onset of dementia by even 2 years also would have significant economic and societal benefits (Brodaty et al. 2011).

Multidisciplinary research supports targeting the vascular pathway for intervention against dementia. Control of smoking, high blood pressure, high cholesterol, obesity, and diabetes, especially from middle age, are the major intervention measures to achieve primary prevention for dementia. This is possible because most lifestyle and metabolic risk factors are modifiable or amenable to prevention and treatment. For instance, intervention studies have demonstrated that diabetes, hypertension, and obesity can be prevented by modifying lifestyles (e.g., dietary habits and physical exercise) (Fratiglioni and Qiu 2013). Thus, intervention measures targeting these lifestyle and metabolic risk factors from middle age are likely to reduce risk of dementia. Furthermore, preventing recurrent cerebrovascular disease and maintaining sufficient cerebral perfusion by adequately managing cardiometabolic risk factors, such as diabetes and hypertension, also may help postpone clinical expression of the dementia syndrome.

Indeed, the achievements in understanding the major modifiable risk factors and possible mechanisms for dementia have so far not yet been successfully translated into intervention programs against the disease, owing to several reasons such as targeting only a single risk factor and implementing the intervention in the improper time-window (e.g., later in life) over the lifespan (Qiu 2012). The unsuccessful preventative and therapeutic trials on dementia also call for new strategies

in future intervention studies. Several intervention programs are currently being tested in Europe to see whether interventions targeting modifiable lifestyles and major metabolic risk factors are effective in delaying onset and progression of symptomatic dementia. These trials implement a multi-domain intervention approach, with cognitive outcomes and dementia as primary endpoints. It is highly expected that the ongoing intervention studies may shed new light on the etiology and prevention of symptomatic dementia.

11.5 Conclusion

As population ages, dementia has become a major public health concern worldwide due to its adverse impact on functional dependence, quality of life, institutionalization, and mortality. Dementia is treatable, but not curable. Thus, intervention programs targeting major modifiable risk factors to postpone onset of dementia syndrome are essential to reduce its tremendous societal and economic burden. Evidence has been accumulating that unhealthy lifestyle and metabolic risk factors at middle age or later in life are associated with an increased risk of dementia. The biological plausibility for these lifestyle and metabolic risk factors being involved in the onset, expression, and progression of the dementia syndrome also is largely supported by neuroimaging and neuropathological studies. Thus, from a life course perspective, adequate management of major cardiovascular risk factors and related vascular diseases starting from middle age may be one of the most promising preventative strategies against late-life dementia and cognitive decline.

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Part III
Promoting Health, Cognition, and Well-Being in Old Age Through Care and Interventions

Chapter 12
Understanding Long-Term Care Outcomes: The Contribution of Conventional and Behavioral Economics

Birgit Trukeschitz

12.1 Introduction

Aging societies are confronted by a growing need for adequate and reliable long-term care (LTC). Policy makers, LTC service commissioners, and providers face challenges in securing appropriate LTC, not only in terms of funding but also in terms of monitoring its effectiveness and efficiency. Identifying cost-effective LTC interventions has attracted increasing interest, particularly against the background of limited financial means.

Economists support policy makers and care service managers in identifying the effects of LTC policy interventions/service designs and assessing whether such measures are worth their cost. Contrary to popular belief, economic evaluations are thus not only about clarifying how much money is needed to fund LTC interventions or minimizing cost. They also seek to properly capture the outcomes of LTC, such as the effect of LTC on care recipients' well-being or quality of life (QoL), so that "costs and benefits" or "costs and effectiveness" of interventions can be compared and used to aid decision-making.

Although conducting evaluations to indicate value for money may be considered routine work for economists, there are still methodological challenges. Challenges in identification, measurement, and valuation of effects (Brouwer et al. 2001; Byford and Sefton 2003; Raftery 2000) arise particularly in evaluation studies that involve dependent and vulnerable people. More specifically, LTC outcome measurement becomes demanding if the cognitive capacities of care recipients are limited and crucial outcomes of LTC services or other interventions are intangible. In the last few decades, approaches and techniques for conducting economic

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evaluations in health care and LTC have been further developed and refined to capture more accurately what is important to LTC recipients and their carers and to gain greater precision in measurement.

Recent developments in LTC outcome measurement build on the findings of various disciplines and different schools of thought within disciplines. Disciplinary backgrounds shape the way we define and approach problems and influence the paths we take to solve them. Considering ideas and concepts from various strands of theoretical thoughts within a discipline, as well as integrating different disciplinary approaches, enables us to better understand LTC outcomes. Promising approaches that enrich conceptual and theoretical reasoning on the nature and measurement of LTC outcomes have been found in the work of Sen (1985) on capabilities and functioning, in hedonic psychology, and in cross-disciplinary fields, such as QoL research (Forder et al. 2007; Netten 1993a).

This chapter focuses on economic contributions that aid both our understanding and the measurement of LTC outcomes. First, it aims to clarify the concept of LTC outcomes using a production-centered approach. Second, it discusses the challenges of measuring them by referring to two economic approaches: (1) conventional economics, represented by mainstream neoclassical economics and theoretical enhancements incorporating the characteristics of LTC, and (2) selected insights from "behavioral economics", a strand of economic thinking that builds on the findings of psychology and other disciplines.

This chapter is set out as follows. Section 12.2 clarifies the concept of LTC outcomes, building on a production-centered approach. Section 12.3 introduces the basic characteristics of conventional economics and behavioral economics. Drawing on both strands of economic literature, Section 12.4 discusses the challenges of measuring final LTC outcomes, in light of these theoretical foundations. Section 12.5 introduces approaches to measuring, and Sect. 12.6 summarizes the findings and draws conclusions.

12.2 Defining LTC Outcomes Using a Production-Centered Approach

Although the term "outcome" is quite well defined in scientific contexts, particularly in health economics, it becomes blurred and poorly understood when used in other contexts. Policy makers, regulators, and providers as well as older people and their informal carers often struggle to grasp the meaning of LTC outcome and to use the term in a consistent way. Qureshi et al. (1998: iv) pointed out that "the language of outcomes was unfamiliar to many older people and their family carers, as well as to many staff in social care services." In addition, thinking in terms of outcomes requires a process of reorientation of LTC providers (Nicholas and Qureshi 2004: 10). Malley et al. (forthcoming) reported that the meaning of LTC service outcomes in an administrative or regulative context differs considerably from the scientific understanding. Moreover, with the exception of a few countries, such as England,

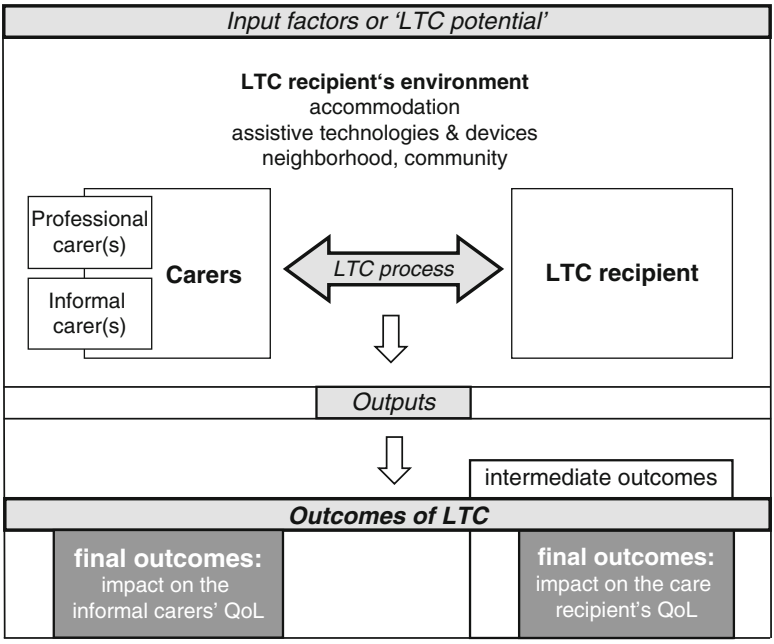

Fig. 12.1 LTC outcomes in an LTC production framework

outcome-related LTC regulation is in its infancy. Regulation and evaluations still relate mainly to input characteristics, such as room sizes, equipment, and staff qualification (Malley et al. forthcoming; Trukeschitz 2010). Clarifying what is meant by LTC outcomes and how to measure them is essential for a fruitful discussion that shifts the attention of LTC regulators, providers, users, and other stakeholders onto the impact of care interventions.

Applying a production-focused approach (see Fig. 12.1) enables us to distinguish "outcomes" from "outputs." LTC outcomes are defined as the *end results* of care and support provided for a person who is no longer able to cope with activities of daily living (Netten 1993b; Knapp 1984). LTC outcomes thus relate to the effects of an intervention. By contrast, "outputs" refer to the service activity itself and are usually measured by the units of services provided, for example, hours of home care, or number of day care sessions (Malley and Fernández 2010; Knapp 1984).

As Fig. 12.1 shows, various input factors, such as informal care, professional care, and home environment, are combined to produce outputs and achieve outcomes. One of the most important generic characteristics of personal services in general and LTC in particular is that these services are *simultaneously produced and consumed* (Baldock 1997), which is known as the "uno actu principle" of services. Production and consumption of LTC are intertwined, as care recipients and their environments become part of the production process (Trukeschitz 2011). Consequently, LTC outcomes depend on the care recipients' willingness and ability to collaborate as well as on the characteristics of their homes.

Outcomes can be further differentiated into "intermediate" and "final" outcomes. "Intermediate" LTC outcomes refer to specific states, behaviors, or perceptions of care recipients that may be influenced by the care intervention. Corresponding LTC outcome measures often comprise detailed sets of care-impact-related indicators, e.g., degree of hydration or nutrition, development of bedsores, or the impact of care on self-care abilities. A comprehensive collection with detailed descriptions of such outcomes can be found in the "Nursing Outcome Classification (NOC)" (Johnson et al. 2005). Another interpretation of intermediate outcomes refers to changes in services (Qureshi et al. 1998: 3). In this line of reasoning, an intermediate outcome of home care, for example, might be whether admission to residential care could be avoided, maintaining people in their own homes (Netten 2011). Intermediate outcomes influence final outcomes but do not indicate to what extent LTC affects QoL.

"Final" LTC outcomes, by contrast, go beyond the intermediate consequences of LTC and aim to reflect not only the ultimate effect, influence, or impact of care (Knapp 1984: 31; Qureshi et al. 1998) but also the value of the effect (Malley and Fernández 2010). Most common concepts measuring *final* outcomes of health and LTC interventions relate to individual well-being or QoL. QoL approaches are applied to reflect the actual consequences of a health or LTC intervention on the individual's life. QoL domains need to be carefully chosen in order to obtain a measure that appropriately reflects the effect of care on the recipients' QoL. Concepts such as "care-related quality of life" (Vaarama 2009) and "social care-related quality of life" (SCRQoL) (Netten et al. 2012a) are built on these considerations (see Sect. 12.5).

Depending on the aim of a piece of research, it might be useful to focus on outputs, intermediate outcomes, and/or final outcomes. An investment in home care services, for example, can be analyzed by counting the hours of home care being consumed (an output), whether specific conditions, e.g., bed sores, could be reduced, or by evaluating the effect of home care on the rate of care home admissions (intermediate outcomes) or, more generally, by investigating the impact of LTC on care recipients' QoL (final outcome). In order to determine the impact of the investment and derive valid conclusions, outcome indicators need to be chosen that correspond to the goals of the analysis.

Measuring LTC outcomes requires not only the identification of effects of LTC interventions. Effects can also be considered in terms of the utility they create. According to Netten and Davis (1990), LTC generates utility in two ways. It can be derived from the *results* of LTC, for example, people feeling clean and presentable, living in a clean and comfortable environment, being fed, or having other needs met. People also derive utility from the *care process* itself. This process utility is influenced by both the way care is provided, for example, whether it is friendly and responsive and whether people experience any utility or disutility by having a certain task done for them instead of doing it themselves.

Building on the work of Sharp (1981), Netten and Davis (1990: 334) illustrated the latter for activities in a care recipient's household, such as cooking. If a meal is prepared, the care recipient will no longer experience the joy as well as the burden

of cooking. Thus, if a family carer, care worker, or "meals on wheels" service takes over meal preparation, the effect on the recipient's utility will depend on whether cooking used to be a joyful or burdensome experience. When cooking was a pleasure, having others prepare the meals will decrease the utility. If, on the other hand, they found cooking burdensome, having it done by others will increase their utility, independently from the outcome-related utility derived from a cooked meal. Thus, both sources of utility, results and related processes, matter and need to be considered for QoL outcome measurement.

One more extension is needed for a comprehensive analysis. So far, the focus has been on LTC outcomes for care recipients only. However, LTC may also affect other groups of people, such as carers and employers of informal carers (Schneider et al. forthcoming; Schneider et al. 2013; Trukeschitz et al. 2013) as well as other social security systems. Malley and Fernández (2010) expanded the focus of outcome measurement by discussing the implications of the "presence of caring externalities." In economics, externalities refer to activities that affect other subjects without either compensating them for any negative effects or charging them for positive spill-over effects. Benefits and drawbacks of professional care, for example, may affect not only service users but also their care networks, particularly the well-being of informal carers (Malley and Fernández 2010: 565). Some LTC services, such as day care services providing care, occupation, and enjoyment for older people during the day outside their homes, aim to support dependent people *and* their carers. Day care centers generate benefits for both care recipients and carers, who may both enjoy spending time apart. Thus, if we seek to capture the full impact of LTC, that is, the full consequences of service provision (see Fig. 12.1), QoL states of informal carers will also be of interest (for QoL domains for carers, see Nicholas and Qureshi 2004; Qureshi et al. 1998; Rand et al. 2012).

12.3 Conventional and Behavioral Economics: The Basics

Against the background of economic theory, LTC outcomes can be considered as the impact of care services or interventions on a person's well-being, which in economics terms is reflected by the concept of "utility." If we knew a care recipient's utility function, that is, how the goods and services contribute to their utility, then we could directly measure how LTC affects their welfare. In line with the mainstream school of economic thought, Samuelson (1948) suggested that utility can be inferred from rational choices people make in perfect markets, given their budgets. It is important to note that utility does not need to be directly measured. Ranking choices is sufficient to indicate that a good or service is preferred to others (Forder et al. 2007).

LTC, though, is hardly allocated by perfect markets (Knapp 1984). Markets do not exist for all possible interventions. For example, care provided by family members and friends is not traded on markets and thus does not have a market price. Moreover, for various reasons, markets for LTC services do not work efficiently or

produce undesirable results (Trukeschitz 2006; Forder et al. 2007). As a result, they are often publicly regulated. Governments, for example, provide cash benefits that increase people's purchasing power, subsidize service provision, or purchase care on behalf of care recipients. Prices in these "quasi-markets" (Le Grand and Barlett 1993), if they exist at all, often no longer appropriately reflect the impact of the service on a user's utility. Alternative approaches are needed to determine the effect of LTC on well-being.

More generally, the explanatory power of neoclassical economic approaches to *predicting* human behavior has been challenged. Human behavior that systematically deviated from predictions by the standard model led scholars to revisit the core neoclassical assumptions to decision-making behavior, mainly rationality, willpower, and self-interest, by taking into account the findings of other disciplines, particularly psychology. Wilkinson and Klaes (2012: 13) recalled that "for much of its history, economic thought has evolved in close proximity to psychological reasoning." Essential contributions to the development of economic thought based on psychological foundations date back to the classical economists (e.g., Adam Smith, Jeremy Bentham) and can be found sporadically in the first half of the twentieth century, gaining momentum in the 1950s and 1960s (Wilkinson and Klaes 2012: 13). At the end of the 1970s, the work of Kahneman and Tversky (1979) and Thaler (1980) attracted the attention of psychologists and economists (Wilkinson and Klaes 2012: 14), who have further developed both these ideas and previous attempts to underpin economic thinking with psychological reasoning into a strand of economic literature, known as "behavioral economics."

Behavioral economics takes up ideas of hedonic psychology and other disciplines, including other social sciences and biology, particularly neurosciences. It seeks to provide a conceptual foundation that refines standard approaches to modeling economic human behavior (Wilkinson and Klaes 2012). Behavioral economic approaches address human limitations in decision-making by introducing the concepts of "bounded rationality," that is, behavior resulting from limited cognitive capacities as well as restrictions in time and barriers to information, "bounded willpower," which reflects choices that are not in a person's long-term interest and "bounded self-interest" which explains behavior that sacrifices an agent's own interest (Mullainathan and Thaler 2000).

Detailed insights have been gained into the mechanisms of all three "bounds of human nature" (Mullainathan and Thaler 2000). Among the mechanisms leading to "boundedly rational behavior," most attention has been drawn to heuristics (i.e., shortcuts for decision-making, "rules of thumb"), factors that unconsciously influence choice by the way information is presented (e.g., frames), internal processes that influence the level of happiness (e.g., adaptation and the implications of aspirations), and the role of emotions and limitations of the human brain that may lead to systematic miscalculations and incorrect predictions (Wilkinson and Klaes 2012). People's abilities to predict the outcomes of their choices have also been critically reviewed (Kahneman and Thaler 2006). "Bounded willpower" is reflected by self-control problems that may result in the sacrifice of long-term goals for immediate gratification.

Self-control problems, such as procrastination, can be explained by time-inconsistent or context-inconsistent preferences (Ariely and Wertenbroch 2002). "Bounded self-interest" has been discussed in the context of benevolent behavior and selfless actions as well as for situations where people favor punishing unfair behavior even at a cost to themselves. To be more explicit, behavioral economists argue that generic characteristics of human nature mean people do not strictly act in accordance with the assumptions of neoclassical economics.

Considering behavioral economic approaches may improve our understanding of LTC outcomes and their measurement in two ways. Behavioral economics offers alternative approaches to interpreting observed LTC outcomes. It also has the potential to advance our understanding of decision-making processes and the challenges relating to specific aspects of measuring LTC outcomes (see Sect. 12.4).

12.4 Challenges to Measuring Final LTC Outcomes in Light of Conventional and Behavioral Economics

12.4.1 Decision-Making on LTC and Its Implications for Outcome Measurement

According to conventional economics, LTC outcomes reflect the consequences of rational, utility-maximizing behavior, meaning that care recipients have chosen the type and amount of care that maximizes their well-being, given their budgets. The decision rule for rational choices requires comparing the marginal benefits of care, that is, the additional satisfaction related to the consumption of one additional unit of care, with the marginal cost, the additional cost of this unit of care. If the marginal benefit is equal to the marginal cost, then the chosen amount of care will maximize the dependent person's satisfaction (Pindyck and Rubinfeld 2013: 87). Behavior characterized by such rational decisions, full power to exercise one's will, and self-interest is expected to lead to "optimal" choices for the decision-makers, given their budget restrictions.

The *decision-making process* for LTC deviates from other goods and services which raises concerns about whether the choice of a specific care arrangement and the resulting outcomes reflect the care recipients' "true" preferences for various reasons. First, it is doubtful whether care recipients always decide on the type and amount of LTC on their own. Family carers may influence or even choose the care arrangement, e.g., the use of professional care services. In doing so, they may follow their own interests, which do not necessarily correspond to maximizing the well-being of the person in need of care. In the case of informal care, the care recipient must rely on whatever type and amount of care family members or friends are willing to provide. Therefore, in a nonmarket setting, the care arrangement is negotiated between care recipients and their informal carers rather than chosen by the care recipient alone.

Second, the nature of LTC service provision makes it difficult to predict the utility that will result from a specific care arrangement. The care recipient and/or their carers may choose the type of care service and the care organization, but they are rarely able to choose a specific care worker. Indeed, carers' complaints often relate to frequent changes of care workers (Trukeschitz and Michalitsch 2011). The care process in general and the relationship between care worker and care recipient in particular are crucial for achieving acceptable LTC outcomes. As neither results nor input or process characteristics can be effectively controlled by the LTC recipient, it is hardly possible for them to fully anticipate the outcomes of decisions about care arrangements.

More generally, behavioral economics states that, by and large, people have difficulties in predicting their experience of hedonic outcomes of their choices. Their forecasts of such outcomes are influenced by their current emotional state, the context of choice, their potentially biased memories of past experiences, and flawed predictions of adaptation to changes in life circumstances (Kahneman and Thaler 2006). For example, Baldock (1997: 86) noted that recipients' or carers' "plans will reflect their hopes, or their pessimism, rather than informed judgment." As predicting possible outcomes is challenging, being subject to both predictable, if large, uncertainty, and cognitive biases that impede maximizing utility in expectation, it is doubtful whether optimal choices can be realized.

Decisions about care arrangements may be affected by actual or perceived social norms, for example, staying at home being preferred, as well as by actual or perceived social taboos, for example, that a frail mother should live with her children and not in a care home. Some people will decide on a certain care arrangement based on whether other people have adopted it. A person's decision may follow or mimic other people's choices, reflected in the concepts of the *bandwagon effect* (Leibenstein 1950) or *herding behavior* (for illustrations, see Ariely 2009). In some cases "keeping up with the Joneses," not falling behind neighbors or others, may also influence choices. If the peers of either the care recipient or carer rely, for example, on informal care only, these effects would lead us to assume that the person deciding on the care arrangement will be tempted to follow suit. Thus, decisions about care arrangements may be context dependent.

As a matter of principle, behavioral economists perceive the *behavioral norms* underlying rational decision-making as critical. Deliberative, carefully calculated decisions that are not affected by emotions and other influences are assumed to be the exception rather than the rule. These deviations from rational behavior are twofold: people might simply choose not to follow these strict norms essential for rational behavior and they cannot always engage in such calculation-based decision-making. People in need of LTC, in particular, may suffer not only from physical but also from cognitive or intellectual limitations, which may restrict their ability to make deliberative, carefully calculated decisions about their care arrangements. They thus face considerable difficulties in maximizing their utility by choosing the best care they can afford or by intervening when care is not provided according to their wishes. However, behavioral economists argue that even with average cognitive or intellectual skills, choices may deviate from the predictions of the standard model

as decisions may be affected by people's emotions (Loewenstein 2000), subject to cognitive illusions, meaning the way in which information is presented affects their understanding, or governed by heuristics (Tversky and Kahneman 1974; Kahneman and Tversky 1996). People may therefore try to make optimal decisions but end up with a decision-making behavior known as "satisficing" (Simon 1956) that risks results that are second best or worse. Care recipients, therefore, may choose and even stick to a care arrangement that does not perfectly fit their limitations and living conditions. Consequently, we should be aware that we do not always observe the best possible LTC outcomes, that is, optimal levels of met needs or QoL states given the available budget, but rather results that reflect room for improvement.

An awareness that observed LTC outcomes may differ from optimal, utility-maximizing outcomes has considerable implications for both LTC outcome measurement and policy. Given the restrictions on utility-maximizing behavior in general and in the LTC setting in particular, measurement approaches that rely on revealed-preference techniques by inferring people's preferences from their choices will be misleading. Moreover, suboptimal results imply leeway for LTC policy to correct the outcomes by influencing those factors that hinder the achievement of the best possible results.

12.5 Implications for Subjective LTC Outcome Measurement

As revealed-preference techniques have considerable limitations for LTC outcome measurement, researchers often rely on subjective assessments of LTC outcomes and stated-preference techniques, where respondents' statements are used to elicit their preferences. They collect data from care recipients, people who answer on their behalf, or by trained observers, always bearing in mind that judgments and standards of comparison may differ between care recipients, carers, and care workers (Qureshi and Nicholas 2001: 15). In addition, a person might not respond to questions consistently across time, leading to systematic errors (for this "response shift" phenomenon, see Schwartz and Rapkin 2004). Approaches to measuring social phenomena of interest, such as LTC outcomes, thus imply that precision of measurement depends not only on the theories and concepts underpinning a survey or measurement toolkit but also on the behavior of those responding.

LTC outcome measurement that relies on self-assessment tools or observational methods may easily be affected by biases, which can be explained by behavioral economic approaches. First, subjective measures gather information on people's personal judgments or experiences with LTC. The majority of approaches to measuring care-related QoL are survey or observation based and thus capture people's experiences in retrospect, rather than in real time. Kahneman et al. (1997) argue that "instant utility" reported in real time may differ from "remembered utility" reported in retrospective evaluations of past episodes. According to their findings, retrospective evaluations are characterized by sensitivity to experiences representing peaks of

feeling, perhaps pain or joy, and the experiences at the end of the care treatment. As we are interested in the impact on QoL, Kahneman et al. (1997) remind us that the answers to questionnaires collected first-hand reflect the memories of LTC-related utility, and the *remembered* QoL, rather than total or overall utility generated by LTC.

There is considerable evidence in psychological literature that suggests to interprete self-reported QoL scores with caution, even when people responded honestly to a survey. One puzzling finding is that people who experience life with extreme limitations report QoL that is the same or just slightly lower than QoL scores of people in much better circumstances (Albrecht and Devlieger 1999). The underlying phenomenon causing such effects is known as "hedonic adaptation."

Generally speaking, hedonic adaptation refers to some built-in mechanism that stabilizes a person's perception of happiness (perceived subjective well-being) as time passes despite positive or negative experiences that have affected their lives. Happiness research has focused on positive life events, such as the effects of lottery winnings on people's happiness, and revealed that the induced increase in happiness is only temporary. However, hedonic adaptation may also work as a protective mechanism by adapting a person's judgment of QoL to negative effects on life circumstances within a given amount of time. The underlying processes are compared to the biological immune system that protects an organism from the attacks of the outside world (Gilbert et al. 1998). Similarly, the "hedonic immune system" (Gilbert et al. 1998) focuses the individual's attention on the bright side of life (Amundson 2010: 380). In the context of LTC, adaptation helps dependent people to live a happy life despite their impairments. Schwartz and Rapkin (2004) argue that adaptation processes should not be seen as a source of error but rather as integral to the assessment of QoL.

Awareness of adaptation processes is essential in interpreting outcomes of LTC. An observed improvement in a person's QoL could be due to an LTC intervention, but also to adaptation, as the person becomes used to the limitation he/she faces. In addition, LTC interventions not only improve people's living conditions but may also explicitly or implicitly facilitate hedonic adaptation. Whatever the source of adaptation, it might blur observed LTC outcomes, causing us to over- or underestimate the "true" impact of a LTC intervention. This needs to be considered in the way we formulate survey questions and by appropriate methods of analysis (see also Sect. 12.3).

In addition to adaptation to living conditions, *aspirations* are also subject to homeostatic processes that aim to stabilize internal conditions in response to changes in the external environment. Improvements in meeting a person's needs, for example, lead to an increase in well-being or QoL in the short term. As time passes, aspirations may increase as well, and if care recipients' experiences do not keep up with their aspirations, then their satisfaction will return towards its baseline (Forder et al. 2007; Netten 2011). Aspirations may be affected by both experienced outcomes and the way in which care is provided. Care workers and informal carers may considerably influence the care recipient's expectations about what is or is no longer possible for their lives, thereby contributing to raising or dampening expectations. Care recipients thus may not *report* higher QoL, even if they were *experiencing* it (based on Kahneman and Krueger 2006: 16). Reported QoL outcomes might include

such aspiration effects, which make it difficult to correctly attribute the effects of LTC interventions on well-being or QoL.

More tangibly, successful coping strategies may also be reflected in care recipients' self-assessments of QoL. Diener et al. (1999) suggest distinguishing "coping" from "adaptation," as coping requires the care recipient to play an active role, whereas adaptation addresses the automatic biological process. Coping can take many forms. It may relate to spiritual beliefs by drawing strength from faith or reflect a mental attitude that gives events a positive meaning or assigns positive implications to impairments. More generally, Brandtstädter and Renner (1990) identified two coping strategies: "accommodative coping" refers to adjusting preferences to a given situation. This type of coping may be observed when people report high satisfaction with their QoL, despite inferior levels of support. "Assimilative coping," on the other hand, involves actively adjusting developmental and life circumstances to personal preferences. LTC can actively support both types of coping strategies, which also may be reflected in the level of outcome measured.

Finally, subjective assessment of LTC care arrangements may not be independent of context and depends on how the person compares him/herself to others. Gains and losses are evaluated according to a *reference point* (Wilkinson and Klaes 2012: 164ff). It might be the case that the reference point for evaluating LTC-related QoL is not the difference in one's own QoL but rather the perceived QoL of a reference group. Such reference groups can be neighbors or other service recipients who are of the same age or are also frail (for an example, see Trukeschitz and Fliegenschnee 2012: 38). In this case, the subjective assessment by service users or their immediate family is reflecting phenomena other than the impact of LTC on a person's well-being.

Behavioral economics offers several concepts that allow to critically assessing what we are actually going to measure and how the LTC outcomes we observe might be affected by underlying phenomena. It points out that we may only be measuring a certain aspect of experienced utility, "remembered utility," when using self-assessment tools. Moreover, the implications of potential distortions in the assessment of LTC outcomes are far-reaching. If the "true" impact of LTC on QoL is higher or lower than the impact measured, then the effect of LTC will be underestimated or overestimated. Both types of flawed measurement will lead to incorrect policy conclusions about how to improve living conditions of people with long-term conditions.

12.6 Approaches to Measuring LTC Outcomes: Issues and Recent Developments

According to conventional economic theory, it is possible to compare the outcomes of LTC services in terms of utility gained from the consumption of such services. Where there is a market for LTC services, the price for a unit of service is assumed to reflect its added utility to the purchaser. Where there is no such market, as is the

case with informal care, or where prices do not result from perfect competition, a number of alternative methods to measure LTC outcomes come into play.

Research in economic evaluation has developed several indirect and direct ways to assess outcomes when rational choices in competitive markets cannot be observed. One indirect way to value utility-generating services is to use market prices of close substitutes, such as the market price for comparable professional services, when valuing unpaid care. Where this is not possible, economic valuation seeks to measure desired states, such as care-induced effects on clients' levels of met needs in non-monetary terms. Cost-effectiveness analysis then provides information on the cost per unit of the desired outcome.

If the evaluation aims to compare cost and utility, some valuation method is needed. Stated-preference techniques, such as contingent valuation using a willingness to pay approach, or a time trade-off method for preference-based valuation of care-related QoL states, are needed. Both allow the comparison of the economic efficiency of alternative LTC services in monetary terms. However, all these alternatives to revealed-preference methods come with a number of limitations.

Whatever approach is chosen to subjectively measure QoL-effects, it requires a survey of either people's levels of met needs or their well-being ratings. Both come with challenges for empirical investigation, relating mainly to the choice of LTC outcome domains (see Sect. 12.6.1), the methods used to elicit preferences for LTC outcome domains (see Sect. 12.6.2), and techniques for capturing the impact of LTC on care-related QoL (see Sect. 12.6.3).

12.6.1 LTC Outcome Domains

QoL research literature agrees that "quality of life" is a multidimensional construct rather than a single one (Rapley 2003). Domains included in QoL measures differ depending on the purpose of measurement. For health care, instruments are based on the concept of health-related quality of life (HRQoL) and include generic HRQoL instruments, such as the Medical Outcomes Study 36-Item Short Form (SF-36) or the EuroQol Instrument (EQ-5D), as well as disease- or condition-specific instruments (Coons et al. 2000). As LTC differs in its nature from health care, HRQoL-related instruments are not expected to be sensitive enough to capture the effects of LTC on people's QoL (Byford and Sefton 2003). Thus, concepts are required that reflect all and only those QoL domains that can be influenced by LTC (Netten 2011) and which are important to care recipients.

Qureshi et al. (1998) and Qureshi and Nicholas (2001) offer a three-way classification of LTC outcomes that allow the derivation of LTC-specific QoL domains. "Change outcomes" capture effects that relate to *improvements or deterioration of an older person's mental or physical condition*. LTC might explicitly focus on improvements in certain conditions or self-care abilities of the dependent person. However, in general, such improvements are not considered the main goal. Instead,

Table 12.1 Types of LTC outcomes and their domains, from the care recipient's perspective

LTC outcomes relating to…		
…changes in	…maintenance/prevention	…the way services are provided
Symptoms and behavior	Have basic needs met, e.g., being personally clean, adequately fed	Feeling valued and treated with respect
Skills and capacities	Feeling safe and secure	Being in control of how the care is provided
Ability to get about	Living in a clean and comfortable environment	
Confidence and morale	Keeping alert and active, undertaking meaningful activities	
	Experiencing social contact and company	
	Being in control of daily life	

Source: based on Qureshi et al. (1998: 4ff) and Qureshi and Nicholas (2001)

LTC largely aims to compensate the person for the impact of impairments on their life and to maintain their QoL despite any long-term impairments (Malley and Fernández 2010: 566). LTC-related "maintenance outcomes" thus reflect care efforts to *stabilize a person's QoL or minimize its decline*. LTC aims to maintain at least acceptable levels within a set of QoL-related domains, such as safety and social participation, and to ensure, for instance, that people feel and are safe or have the social contacts that they want. "Process outcomes" relate to the impact of *the way LTC is provided*. The care process does not only change or contribute to maintaining a specific physical condition. It also influences care recipients' psychological well-being. The interaction between carer/care worker and care recipient might affect how care recipients feel both about themselves and how much they are in control of the care process. Malley and Fernandez (2010: 564) add that the way care is delivered becomes an integral part of the care recipients' lives because of the continuous and long-term nature of care provision. The specific nature of LTC thus requires accounting for change, maintenance, and process-related effects on QoL in order to capture the total impact of care on a care recipient's QoL (see Table 12.1).

To reflect these specific requirements for QoL measurement in the LTC context, Netten et al. (2012a) developed the "social care-related quality of life" approach. SCRQoL is the core concept of the measurement toolkit ASCOT (Adult Social Care Outcome Toolkit). ASCOT contains seven domains, relating to higher and lower order aspects of a dependent person's life. Lower order domains include personal cleanliness and comfort, food and drink, personal safety, and cleanliness and comfort of accommodation. Higher order domains include control over daily life, social participation, and occupation and dignity (see Table 12.2). All domains match quite closely to Qureshi et al.'s (1998) conceptual approach of LTC outcome categories for maintenance/prevention and the way in which services are provided.

Table 12.2 SCRQoL-domains, from the care recipients' perspective

Domain	Definition
Control over daily life	The service user can choose what to do and when to do it, having control over his/her daily life and activities
Personal cleanliness and comfort	The service user feels he/she is personally clean and comfortable and looks presentable or, at best, is dressed and groomed in a way that reflects his/her personal preferences
Food and drink	The service user feels he/she has a nutritious, varied and culturally appropriate diet with enough food and drink he/she enjoys at regular and timely intervals
Personal safety	The service user feels safe and secure. This means being free from fear of abuse, falling or other physical harm and fear of being attacked or robbed
Social participation and involvement	The service user is content with their social situation, where social situation is taken to mean the sustenance of meaningful relationships with friends and family, and feeling involved or part of a community, should this be important to the service user
Occupation	The service user is sufficiently occupied in a range of meaningful activities whether it be formal employment, unpaid work, caring for others, or leisure activities
Accommodation cleanliness and comfort	The service user feels their home environment, including all the rooms, is clean and comfortable
Dignity	The negative and positive psychological impact of support and care on the service user's personal sense of significance

Source: http://www.pssru.ac.uk/ascot/domains.php (accessed 12 Oct 2013)

12.6.2 Accounting for the Relative Importance of LTC Outcome Domains

To reflect the various possible effects of LTC on people's lives, an outcome measure is needed that covers several domains. To obtain a single measure requires aggregation of the values across all domains and accounting for the relative importance people put on each of them. Some may prefer, for example, feeling safe to having sufficient contact with people. Others may prefer the opposite. The relative importance of outcome domains reflects people's preferences for different LTC outcomes.

Achieving maximum scores on all care-related QoL domains is not always possible, given trade-offs, nor should be assumed that care recipients seek to achieve maximum scores on each domain. The underlying reasoning of the domain "control over daily life" is illustrated by a quote from Schooler et al. (2001: 66) cited in Wilkinson and Klaes (2012: 483): "The challenge is determining when it is best to man the controls, and when it is better to simply enjoy the ride." Maximum control over daily life, for example, is not necessarily a desired outcome, but ensuring a person achieves their desired level of control seems relevant.

Questions about how to elicit preferences arise in two areas: how to measure preferences and whom to ask, whether care recipients, carers, or the general population. As in LTC revealed-preference methods way lead to biases (see Sect. 12.4.1), stated-preference techniques are a sensible alternative. Among the stated-preference techniques, the best–worst scaling approach, where respondents indicate their most and least preferred items out of a list of several items, is currently considered the state-of-the-art approach, as it has been shown to lead to similar patterns in preferences when compared to discrete choice experiments, while being less burdensome for respondents (Potoglou et al. 2011). Decisions about which preference weights to use depend on the aim of the survey. If it is argued that weights should reflect the preferences of the taxpayers who contribute to publicly subsidized services, then it is suitable to use the preferences of the general population. On the other hand, behavioral economic considerations would allow hypothesizing that different experiences with limitations in the general population and in the population of LTC users would affect their judgments. Differences might be due to, for example, endowment effects such as the aversion to lose, for example, independence. Interestingly though, findings for England revealed no differences between the preference patterns of users of equipment and other social care services and the general population (Netten et al. 2012a).

12.6.3 Measuring the Impact of LTC on QoL

It is essential to understand the difference between measuring care recipients' current QoL and measuring the *impact* of a care intervention on the care recipients' QoL. The first requires identification of quality-related areas of life and appropriate scales for measurement (as discussed in Sect. 12.1). The second aims to measure a care-induced change in QoL. Measurement over time might reveal improvements or declines in QoL states. However, these methods only allow us to observe changes in conditions over time (Qureshi and Nicholas 2001: 15) and the comparison between the current and ideal states, if defined. According to Dimitrov and Rumrill (2003), changes of QoL in such a pretest–posttest design can be due to a "treatment effect" of LTC, a "trend effect" caused by developments of the person during the pretest–posttest time period, and a "response shift," which is a change in internal values or concepts of QoL over time as discussed above in reference to the adaptation effect. Sophisticated ways of modeling (see, e.g., Dimitrov and Rumrill 2003; Schwartz et al. 2013; Flynn et al. 2013) are required to disentangle these effects and to uncover what is chiefly of interest, the treatment effect of LTC.

Measurement tools of LTC final outcomes need to capture the *contribution of LTC to the care recipients' QoL* or whether the care a person receives makes a difference to his/her QoL. To investigate this contribution, it is essential to compare the current QoL state of a person receiving care to a *counterfactual*, i.e., someone not in receipt of care (Knapp 1984: 31; Forder et al. 2013).

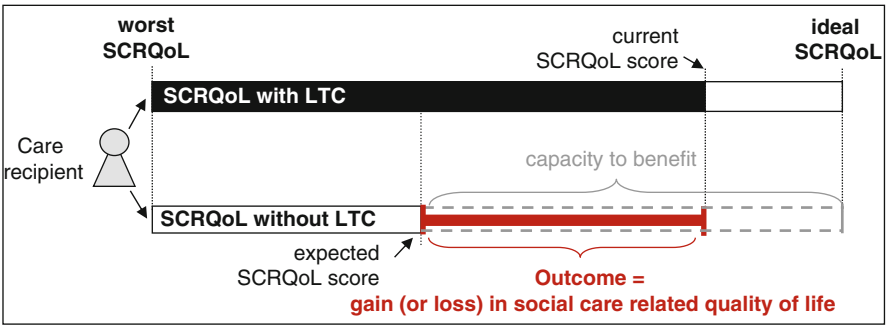

Fig. 12.2 Identifying QoL-LTC outcomes and measuring the impact of LTC on SCRQoL. *Source*: built on the conceptual approach of Netten et al. (2010) and Netten (2011), *Note*. QoL outcome of LTC = SCRQoL gain/loss = current SCRQoL − expected SCRQoL

Figure 12.2 builds on the work of Netten et al. (2010) and Netten (2011) and visualizes the idea of measuring LTC outcomes. The black bar indicates the care recipients current SCRQoL, a state achieved with LTC. The score can take any value between the worst and the ideal QoL state. Measuring QoL by established measures, such as SF-36 or EQ5D, usually ends at this stage. However, as argued above, capturing outcomes also requires information about the counterfactual state, i.e., the QoL if the same person had not received any LTC. Figure 12.2 indicates this second measurement approach by the white bar, labeled "SCRQoL without LTC." The difference between the ideal SCRQoL state and the state a person would achieve without any help is called the "capacity to benefit" from LTC interventions.

The outcome of LTC, i.e., the gain/loss in care or SCRQoL due to LTC, can be seen from Fig. 12.2 and calculated by the difference between the two QoL scores, "current SCRQoL" (the level of QoL with LTC) and "expected SCRQoL" (the level of "SCRQoL without LTC").

The idea behind this concept of outcome measurement is that the observed current QoL has two components: the QoL a person achieves from his/her self-care and the QoL that is added by the LTC intervention. Singling out the LTC-induced part of observed SCRQoL enables identification of the outcome that can be assigned to LTC.

There are several approaches to gathering information on counterfactual states which try to tackle the problem that a person cannot both receive and not receive a service. Study designs using a treatment and control group in which people are randomly allocated to one of the groups, known as "randomized controlled trials," or RCTs, are perceived as the gold standard. Appropriate analytical techniques include difference approaches, regression discontinuity design, and matching (Gertler et al. 2011; Rossi et al. 2004). However, RCT designs are not always possible, particularly in the LTC context, for ethical reasons (Byford and Sefton 2003; Forder et al. 2013). Baldock (1997) even goes one step further, arguing that health-care treatments differ in their nature from LTC, so that the medical model may not be transferable to social care. Alternatively, one can resort to a thought

experiment, for example, by asking care recipients to judge their QoL in absence of the LTC service or fieldworkers to judge how the care recipients would fare without these services (Netten et al. 2010; Netten et al. 2012b) or by inferring "expected SCRQoL" from data on needs of care recipients (Forder et al. 2013).

12.7 Summary and Conclusions

Public spending on LTC is expected to increase sharply over the next 20 years, adding to pressures on government budgets. As a result, LTC policy, like other policy areas, will be under increasing scrutiny. For the sake of those in need of LTC services, it is essential to be able to identify and measure policy outcomes. LTC outcomes provide information on the effectiveness of care and enable policy makers and care providers to compare alternative LTC services. In addition, they enable cost-effectiveness and cost-benefit analyses, which help during the selection of the most efficient among the effective LTC services.

This chapter contributes in three ways to the understanding and development of outcome measures in LTC. First, it clarifies the concept of LTC outcomes, defined as the impact of LTC services or interventions on a person's behavior, perception, state, and, ultimately, his/her QoL. LTC outcomes can be identified for care recipients but also for family carers or even other groups, including employers of family carers. A full economic assessment of LTC services from a societal perspective would have to account for a 360° perspective of such possible outcomes.

Second, this chapter discusses the conceptual approaches in conventional economics to measuring and valuing LTC outcomes, as well as caveats to such approaches from the perspective of behavioral economics. Conventional economics suggests applying revealed-preference approaches to derive the utility of LTC services to care clients. These approaches presuppose that the services in question are traded on fully competitive markets, where rational and utility-maximizing care clients choose their preferred LTC services. Given these conditions, the price paid for a unit of service reflects the gain in the purchaser's utility and hence provides an accurate monetary estimate of the final LTC outcome. When there is no competitive market for the LTC service, then prices either do not exist or are distorted. In addition, care clients' observed choices on existing markets may not be well informed, independent, or utility-maximizing. For these reasons, stated-preferences methods, which are survey-based and seek to elicit care clients' preferences, have been used as an alternative approach.

Insights from behavioral economics fundamentally challenge revealed-preference methods. They also point to a number of potential biases that may affect subjective assessments of care-related QoL and stated-preference methods. According to this strand of economics, people may choose to satisfice rather than maximize outcomes, implying, for example, that observed purchase decisions on LTC service markets cannot be taken to reflect utility-maximizing choices. Behavioral economics also points to framing effects, which could affect the way in

which relevant information on LTC services is accounted for, or bandwagon or herding effects. At the same time, behavioral economists suggest that surveys, including those on care-related QoL, should be interpreted with caution, because of adaptation and aspiration effects, among other factors.

Taken together, while there are multiple approaches to measuring LTC outcomes, they all appear far from perfect. Behavioral economics has its merits in highlighting potential flaws in LTC outcome measurement. Unfortunately, it fails to provide an innovative "third" way of LTC outcome measurement. However, considering the critical points raised by behavioral economists could help to improve the methods, specifically those involving self-assessment and stated preferences.

A third contribution of this chapter was to detail three core issues that have to be addressed when measuring LTC outcomes: (1) choosing LTC outcome domains to be considered in the evaluation, (2) deciding on whether to weight these domains using preferences and, if so, whose preferences to use, and (3) how to attribute effects on a care recipient's QoL to LTC services. This last issue is a major challenge in impact evaluation and hinges on establishing a convincing counterfactual, that is, what outcome level would have been achieved had the care recipient not used the service in question. This and other questions still call for innovative answers, as European societies strive to establish LTC systems that will better meet demand and secure the QoL of tomorrow's older dependent population.

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Chapter 13
Alzheimer's Disease, Patients, and Informal Caregivers: Patterns of Care in France, Sweden, and Greece

Anastasia Meidani

13.1 Methodological System

Presented here are the results of a field study conducted in three sites (France, Sweden, and Greece) between May 2008 and September 2011 involving patients with Alzheimer's disease and their caregivers. The patients in our samples have followed specific institutional paths of care, which both link and differentiate them and allow for comparisons to be made. For example, the patients received specialist professional attention and have access to professional resources that others do not have. Such resources include individualized monitoring, which has an important influence on the type of care provided. At the Greece site, the professionals involved in this study worked for the *Hellenic Alzheimer's Disease Association* in the *Home Help* program and in the *Help Centre for Problems Linked with Alzheimer's Disease*: *Saint Helena*. At the France site, the majority of healthcare professionals worked in the *Memory Centre* of a Toulouse hospital. At the Sweden site, the data were collected in two care centers or "healthcare settings" in the municipality of Norrköping: the geriatrics clinic at the University of Linköping and the geriatrics unit of Vrinnevi Hospital.

Mention should be made of the fact that this research and data collection took place months and sometimes years after the initial diagnosis of Alzheimer's disease had been made: an average of 5 years for France, 2 years for Greece, and less than 2 years for Sweden. Regarding the site, the subjects were either "survivors" or people whom the pathology had affected relatively recently (Sweden) and who had not yet developed the clinical symptoms seen in the later stages of Alzheimer's disease. Thus, in France, where data collection commenced 5 years post-diagnosis, the collection of subjective data from these patients was hampered by communication

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problems, aphasia, or anosognosia. In the Greece sample, the data were collected directly from patients whenever possible (e.g., in half of the cases). Similarly, in the Sweden sample, because of relatively recent diagnoses having been made in the early stages of the disease, the interviews were conducted successfully with the patients themselves.

The interviews with the patients were conducted using monographs, which raises the issue of monographs and the legitimacy of the research protocol. This methodological choice forms the departure point of our research: the individuals providing care cannot be considered as separate entities. Thus, the understanding of the positions and actions of these carers[1] is related to the experiences of the patients. These experiences were expressed in the context of the research interviews and through observations of the care situations during consultations or within the subjects' home (Milles and Huberman 1994). In keeping with this departure point, we established specific models, for each of the parties considered here, which were common to each of the three countries. For analysis purposes, each monograph was constructed in two stages: first, through the production of data sheets, which permitted the selection and the designation of concepts, problems, and key indications on the one hand, and, on the other hand, testing of the frequency and distribution of the phenomena observed. In this way, it was possible to cross-reference the two bodies of data arising from the observations and interviews.

The second level of analysis, which could be qualified as transversal, was an attempt to open up some lines of reflection which would allow for the comparison of qualitative data drawn from different groups of informers. At this stage of analysis, the identification of transversal themes between different subjects informed the manner in which our materials were related with each other. Within this systematic elaboration, we considered the whole story from each interviewee and sought to establish a systematic comparability with the data gathered at the other sites. This comparative approach led to the following analysis.

13.2 The Patients

In medicine, as in psychology, there are specific tools used for the diagnosis of Alzheimer's disease, such as the Mini Mental State Examination (MMSE),[2] which evaluates the level of general cognitive functioning in adults. In the absence of specific biological markers for Alzheimer's disease, these tools can identify some of the hallmark deficits seen in Alzheimer's disease, such as deficits in memory, attention,

[1] Although professional caregivers on each site were interviewed, it is beyond the scope of this chapter to discuss their practices and rationales. However, we will discuss the data gathered in the observation sessions and interviews carried out amongst patients and informal caregivers.

[2] There is extensive literature about this evaluation tool. The founding article is Folstein et al. (1975).

orientation, or language. However, while these tests may inform clinicians about patients' cognitive functioning and contribute to an explanation for why she or he participates less actively in their own care, they do not shed light on the interactional modes which govern the care relationship. This fact raises several questions. On an interactional level, what signs, indications, or modes of communication are given, solicited, retained, or ignored? By what means do patients make their voices heard? It seems essential to respond to these questions if we are to elucidate the modes of interaction at work amongst patients who have difficulty with words, either with their expression or in terms of credibility. All these questions highlight the necessity of examining the patient's *illocutionary force*, that is, their capacity to convince their interlocutor that their words are pertinent.[3]

In keeping with these observations, the aim here is to distinguish problems concerning verbal expression from other behavioral problems. The reason for this is, simply, that once the illocutionary force of the patient becomes weakened, the attention that their caregiver provides to them becomes affected less by the feelings expressed by the patient and more by their ways of being and doing in everyday life.

13.2.1 Altered, Reduced, or Nonexistent Discursive Capacities: Patients' Illocutionary Force

An important concept in sociological theories of aging is that of *decline*, which highlights the strategies of adaptation deployed by individuals to maintain their identity despite difficulties provoked by advancing age. *Ultimate decline* refers to when an individual is no longer capable of preserving what constitutes his or her identity, nor to negotiate it or project it into new affects. The concept of decline thus centers on the person who is subjected to these transformations and on the continuity of his or her identity. While these works explore the relational aspects that stem from practical adaptations due to decline concerning the patient's entourage and their environment (Caradec 2005), it also seems necessary to explore the complexity of caregivers' reactions regarding Alzheimer's disease.

In light of this, it was noted during the study that several of the patients interviewed or observed in the context of their consultations in the three countries, while still in possession of their verbal faculties, minimized the gravity of their pathology and reevaluated their priorities. Thus, they downplayed the extent of their memory loss, they set up coping strategies, and they claimed not to feel particularly troubled by their failing capabilities. The statement of Oscar,[4] an 80-year-old Swedish patient, articulates this: "I think I know my limitations, I know what I remember and what

[3] Austin (1979) defines *illocutionary* as any act of language whose effects may be felt by its object.

[4] In accordance with the rules of confidentiality and anonymity, all the first names used in the context of this article are pseudonyms.

I cannot remember (…) I, of course, think that it would be better if I could remember everything but I remember a lot I think (…) Sometimes I can see that, no, I mean, that I need to think a bit more about something and so I write it down very fast." In the same vein, when the researcher encouraged the interviewee to talk about the question of spatial orientation, he claimed not to be troubled by such problems: "In that respect, I have no problems. My head is still working and that is a good thing."

However, if we compare the patient's statements with those of his caregivers and with what is known from his history and medical records, it is no longer possible to take his declaration at face value. Consequently we find ourselves in a situation where the patient is no longer a reliable informant about his own functioning; he is not able to describe accurately and inform others about his own state of functioning. What is even worse than this is that his statements speak against him and become less a communication of his will and his perception of the world and more the starting point for the evaluative work of the caregivers. We see here how the illocutionary force of the patient becomes weakened without their being aware of it. Between two competing perspectives of the situation, it is the patient's perspective that comes off worse, because it is not in agreement with that of his carers.

13.3 The Patient's Capacity for Expression

During our studies in France, we noted the propensity of professionals to influence our perspective concerning the difficulty of carrying out sociological interviews with certain patients whom they designated as being gravely deficient in terms of communication. "You want to interview him/her? You won't get much out of them, but if you want to try… Let me know how it goes!" (a doctor). In Greece, this kind of resistance came predominantly from the families themselves, who sought to protect the patient from a potentially tiring exchange. While it should be recognized that the attitude of these professionals and families was not wrong, it does shed light on their expectations regarding the verbal autonomy of the patients. It also shows how professionals, as experts who receive a population of patients whose daily communication is weak from an illocutionary point of view, can be led to label patients in such a way as to condition the interactions which follow. Of course, the evolutionary nature of the disease encourages constant reevaluation, as illustrated by the fact that the Swedish professionals abstained from labeling patients during the first stages of the disease.

It seems clear that the illocutionary force attributed to the patient is subject to evaluation and varies de facto from one person to another. From this perspective, two conditions determine the care relationship. One condition concerns the efforts made by an informal helper to communicate, support, or relativize a patient's words. The other condition relates to the disposition of professionals to elucidate and listen to a discourse concerning them. However, this requires caregivers to ensure that their interest in care goes beyond simple health and hygiene considerations to take into account the patient's expressive capacities and to understand their feelings.

13.4 Avoiding Giving Information to Patients

Besides the progressive decrease of the illocutionary capacities of their speech, an essential point worth highlighting concerns the level of awareness the patients are permitted to have about their own state of health and the difficulties they experience. This matter has as much to do with the patients' own characteristics as with the difficulties experienced by members of their family when it comes to talking openly with the patients about their disease. At that point it becomes difficult to engage in a relationship based on full recognition of the reasons leading the carers to intervene in a patient's life. Indeed, Alzheimer's disease is a hard disease to talk about. Many carers simply reject any hint or suggestion of the disease. This tendency was particularly noted in France, where the social representation of Alzheimer's disease still associates it with death. Yvonne, who equipped a room at her home for her sick mother demonstrates this openly: "I never talk to her, I can't talk about Alzheimer's disease in front of her, and I don't like people to say in front of her, 'She has Alzheimer's disease.'"

It would be too simple, then, to explain the nonparticipation of the patient in the organization of their own care solely through their progressive incapacity to communicate or through the loss of weight carried by their words. The patient's position in informational exchanges is skewed by the fact that a smaller place is given to their discourse. Often justified in terms of a desire to make things easier for the patient, the attitude of caregivers takes the form of evasion. In this context, a form of collusion is created between informal and formal caregivers, resulting in the patient being put at a distance.

13.5 Beyond Limits of Communication: Other Behavioral Problems

Two types of behavioral problems can be distinguished. The first relates to tasks the patient can no longer perform. The second, more specific factor, relates to problems that are responsible for changes in the patient's personality.

13.5.1 When the Patient Fails to Perform Their Habitual Tasks: Loss

Failure to accomplish everyday tasks, noted amongst patients, fall under three modalities. The patient (a) no longer performs tasks at all, (b) performs them poorly, or (c) does not finish them. When a patient performs a task poorly, for example, driving a car and putting the lives of others at risk, the solution will involve preventing them from performing the task, in this case by preventing them from driving

their car. In other cases, the home is made secure by preventing the use of gas for cooking. It should be emphasized that such interventions, as noted in the three countries, do not aim to renew a disrupted relationship with the world. Rather, they occur in a more coercive manner, forbidding the patient an activity whose pursuit is judged to be abnormal. Nevertheless, even a disrupted link to the world remains a link, whatever judgement may be made about its nature. Thus, the patient may feel blocked from the dynamics of engagement with the outside world, leaving them to feel as if they are "being pushed aside," as a certain French patient pointed out.

13.5.2 The Patient Develops Unrecognizable Behavior

Notably, cases of hallucinations, aggressive behavior, wandering, or even running away are symptomatic of identity disorders. Interviews performed with patients did not reveal, from the patients' point of view, any feeling of loss of identity, with the exception of certain young patients in Sweden. For them, their worst fears were crystalized in the idea of the behavioral problems that the future might bring them. This is what Henry, 59, said: "And I want to be able to know what is going on, I want people around me to tell me what is happening since I think like this… like I am sitting here now but it could be that I am actually not making any sense." The theme of identity disorder is heard above all in the statements of informal carers. "I don't recognize my father any more"; "my mother, who was such a stylish woman"; "this is a man who used to be so enterprising." From an interactionist point of view, these statements show the relational nature of identity becoming troubled with the progress of Alzheimer's disease. What was taken for granted, such as basic reference points on which family relationships were founded, came apart to be replaced by uncertainty, or even suffering, and the pain of loss. This process of personality alteration constitutes one of the main causes of reevaluation of care perceived in its dimension of attention giving. It accelerates the disengagement of the carer and enhances the perspective of putting the patient into the care of professionals.

13.5.2.1 Hallucination Case Study: "The Phantom Family"

We have chosen to give the name "phantom family" to a specific type of hallucination. This hallucination corresponds to episodes during which the confused patient is unable to recognize certain members of their family, "effaces" certain family members from their memory, or mistakes members of their entourage for others. The patients themselves do not have any reflexive discourse concerning these problems of attributed identity. They only learn about this kind of hallucination through what they are told by their caregivers. This redistribution of roles and identities within the entourage is particularly difficult for those close to the patient, since, deprived of recognition, they can feel ignored by the patient or excluded from their world. Such behavior is also disturbing in that it portrays an active and dynamic

patient who seems able to define and give sense to the world around them, except that their definitions do not concur with those of their caregivers. This was expressed by Katerina in speaking about her husband: "Sometimes he takes me for his mother, and that hurts. It makes me furious and sad at the same time."

13.5.2.2 Moments of "Lucidity"

Fleeting, unpredictable, and relatively rare moments of lucidity never cease to surprise those who witness them and find themselves called upon in this way. Data from the Greece site indicated that such moments where patients seemed to recover their spirits and, with a few sentences, renewed contact with their entourage were generally met with humor and a sense of hope. "Oh, sometimes he comes back amongst us, which is always nice… We tell ourselves everything's not lost, that we're not doing all this for nothing." In the data from the site in France, the entourage expressed sadness: sadness for the patient, who suddenly seemed capable of understanding the gravity of their situation, and sadness for themselves because such moments of clarity momentarily undermined the affective distancing that they had developed to face up to the declining health of the person close to them.[5] Unsurprisingly, it was impossible to collect equivalent data from the Swedish site, since these moments of lucidity generally occur in patients who are at an advanced stage of the disease.

As a painful reminder of what has been lost in the relationship with the other, such unexpected revivals of the actor in the figure of the patient come as a test. They oblige the carers to position themselves around the patient's point of view, to judge their own commitment and even, sometimes, to question their decisions. This was the case for the uncle of Henri who, placed in a care home in the Toulouse metropolis, complained after a 3-week silence that his wife had "abandoned" him and thus convinced her to take him back home. Moments of lucidity clearly outline the limits of a relational construction of care which results in viewing the patient as a nonperson (Goffman 1974), that is to say, as an individual whose presence in the exchanges taking place is not ratified by the participant (Détrie 2007).

13.6 Comparison Groups

Comparison groups have an influence on the institutional forms of care taken because they shed light on possible developments in the disease and the risks experienced by the patient. There are guides for action, set up for patients particularly in

[5] We look at this point in detail in the section of this paper dedicated to the carer, under the title: The Idea of Anticipatory Grief.

Greece and France, to provide an alternative to new forms of care that place patients in collective institutions: day hospitals, reception centers, or other specialist institutions. What deters patients is not the idea of collective care in itself. Before this happens, and even when it is due to occur, the problematic factor is the confrontation and comparisons which are made with groups of users and with which the patients will identify.

It should be pointed out that none of the patients interviewed in France or Greece envisaged the possibility of their being placed in an institution, whereas some of the Swedish patients anticipated the move and were prepared for it, as underlined by the following statement: "It is stupid to deny that one is getting older (…) The way things are today, I think one can say that those that become demented are those that are the most vulnerable, compared to those that are still managing on their own. I get the feeling when I have been at XXX (name of a university hospital omitted) for a couple of days that it is probably a good thing to be young in that situation. If it is an old man… it can't be all that great for then one is coming from an environment that is different." The "mirror effect," but also the fact of inscribing one's personal destiny in a collective situation and the consequent closeness to other patients, constituted a powerful motivation for patients. This encouraged them to clarify their expectations, measure their investment, and have a better perception of the effects of their decisions.

13.7 Informal Carers

Including several sites in this study has enabled the definition, amongst informal carers, of a group of criteria which strongly influences the form taken by care and its evolution during the course of the disease. Synthetically, these criteria can be reduced to some main, mostly binary, factors. These are based, in order of importance, on gender, a double proximity, relational and spatial, family history, and the availability of the caregiver. These factors were evaluated according to the caregivers' state of health and their matrimonial and professional circumstances.[6] The criteria retained here have, above all, a relationship to the capacities of caregivers to invest themselves in the care relationship with the patient. If the focus here is on the caregiver's gender, it is because this is by far the most complex factor, which does not in any way invalidate the determining influence of other criteria in the patterns of care given to the patient.

[6] For example, housewives, widows or divorcees who claim to be in good health, are considered as being most available to fulfil the role of principal carer—in the eyes of the entourage as much as those of the patient.

13.7.1 Man or Woman: Distancing from the Role of Caregiver

It is well established in the current scientific literature that the majority of caregivers are female (Meidani and Membrado 2011). The implication of women in care manifests itself in the time spent performing a whole range of tasks, from the heaviest physical ones (like washing) to the most sociable (spending time in the company of the patient). To clarify the different ways in which men and women invest themselves in care, another variable comes into play. This is the relative importance given to seeking help from the formal sector and to the eventual support of secondary caregivers, depending on whether the principal caregiver is a man or a woman. Men will seek outside help more than women, but they do it for specific tasks: housework, meals, and physical hygiene. This difference tends to narrow with the decline in the patient's state, where women catch up with men concerning recourse to outside help. Take the case of Marcel, one of the French interviewees, who states the following about his wife's relationship to washing: "The bathroom, no. In any case, my older daughter has to come there because that's a mania too. She doesn't want to wash herself, she doesn't want to wash clothes…"

This testimony, corroborated by others recorded at all three investigation sites, introduces the idea of distancing from the role of caregiver implied by the execution of tasks made necessary by the disease and indicates that this distancing is greater amongst men than women.[7] Consequently, it would seem more difficult for men than for women to fulfil the role adequately. This is stated clearly by a social assistant in the Greek Memory Centre, who doesn't hide her admiration for men who manage to fill the gap: "I've been impressed by the abnegation of certain men who look after their wife or their mother. When they're not in the habit of this kind of thing, and it's not easy… The way they manage and take care of an old person is really remarkable!"

13.7.2 When the Principal Carer Is a Wife or a Daughter

What the previous extract shows is that, in terms of the skills required to assist a patient, certain people (mostly women) already possess certain skills or just need to update them.[8] When the principal helper is a wife, for example, the distancing from the role of caregiver is low and the continuity high. As Ulla, wife of a Swedish

[7] This distinction is based on the historically determined division of work between men and women, such as described notably by the Male Breadwinner Model developed by women's studies in Anglo-Saxon countries (cf. Orloff 1993).

[8] It should be noted that the caregivers are capable of choosing which skills to develop during the period of care for the patient. It would be wise to examine the modalities of the decision-making. High on the list would no doubt be considerations around the question of "dirty work" (cf. Rimbert 2006).

patient, mentions, “He started losing control of his bowels and when he came home after having missed going to the toilet, it was me that had to clean him up and that is something one is used to and then (…), he isn’t able to hammer a nail or, well, nothing really. I am the one that…if we, for example, have a bottle of wine, it is mostly me that opens it and yeah, well, everything…” Despite the prevalence of the care situation, the organization of life as a couple is, in many aspects, unchanged in comparison with what existed prior to the clinical manifestation of the disease. The distribution of roles within the domestic environment is not fundamentally shaken.

Amongst the families encountered in the field, in cases where there were both male and female family members, the caregivers were always women. The direct consequence of this is that the brothers of the female caregivers were systematically in the background as far as informal care was concerned. In testimonies provided by close caregivers, the brothers and any other sisters are quoted as, at best, helping in an occasional and secondary manner and, at worst, as being either absent, uninterested, or insensitive to the gravity of the situation, as if they kept the disease at a distance, to use the terminology employed by Samitca (2004). Aside from a few rare exceptions, there was no resentment in these statements. This point is worth underlining because, while it may not say much that is new about the relatively pacified nature of patterns of family care, it does confirm the acceptance by carers of their place in these frameworks. The interview carried out with Kerstin, a 75-year-old Swedish patient, illustrates this: “My daughter, the one that lives in XXX (name of the city) is the one that helps…the other daughter she is not that much into gardening, she is more the lady-like or what can I say? She has never cleared out weeds in the garden or anything like that. She is not interested in such things.”

13.7.3 Proximity to the Home of the Patient and Caring as a “Carer”

The proximity of the caregiver’s residence to that of the patient is also an element which facilitates informal care. In light of this, it should be mentioned that in the Greece site, many older adults, particularly widowed women, live in their daughter’s home. These helpers are often divorced women, frequently without stable professional activity. While this situation may be judged to be more economical concerning care, it also exposes the carers to exhaustion.

On the other hand, when the patient and the carer live a large distance from one another, forms of care implying an earlier recourse to professionals tend to be set up. In these cases, the principal caregiver acts more as a supervisor or manager from a distance. Only one such case was recorded in the Greece site, whereas several testimonies suggest that this is the case in the French and Swedish sites.

Another consequence of the carer living far away from the patient is that this situation dictates in a certain manner the rhythm with which caring will be carried out. The story of Christine, who was living in Italy at the time her French mother was diagnosed, is a perfect illustration of this pattern. With a large geographical distance

separating them, the caregiver is often obliged to plan in advance the periods in which they will travel to spend time with the patient. The difference is significant, because during the time the caregiver spends with the patient they are strongly inclined to make the most of it and devote their time with the patient more intensely than would a caregiver living nearby. Instead of a succession of resolutions spaced out across time, we note here a situation of concentration. A large number of decisions will be made and contact with professionals in the formal sector will increase, to reinforce a situation which is meant to remain operational until the next visit, always at the risk of not being able to prevent an accident from happening.

Whatever the situation prior to the start of the disease may be, the person who becomes the principal caregiver will be someone who already occupied an important place in the life of the person who becomes ill. To be somewhat provocative, we could suppose that there is not any real redistribution of roles amongst members of the family when the disease appears. Individuals occupy places that will remain the same when caring for the patient becomes necessary. To summarize, regarding forms of support, the family structure is not reinvented when a family member is diagnosed with Alzheimer's disease but simply reveals its latent configurations; these family members have already had experience in the "career" of a carer for some years. Delphine recognizes this when she says of her mother: "The two of us had always lived in Toulouse, and because she was a widow we looked after her all the time—she came to eat with us on Sundays, came with us on holiday when we went away in the summer. So she's always been part of our life, of our little world. Even though they were close to Mum, my brothers looked after her much less, but they didn't see things the same way, they had their own families first and then they came to visit Mum."

13.8 The Helper, a "Second Victim"?

As long as their flexibility of movement is relatively good, the caregiver functions in the role of a "partner" with the professionals, constructing the system of care alongside them. When this freedom of movement becomes exhausted, the carer is no longer able to fulfil the growing needs of the patient. Talking about her husband, a Swedish patient says: "As long as my husband is there and has the energy necessary it isn't a problem. But then again, it is as I say sometimes, sometimes he is worse off than me actually, if I say so myself." It is then necessary to care for the caregiver, who becomes a "secondary" object of formal care, in that part of the professionals' activity will be to evaluate the caregiver's state of health and take whatever measures are necessary to support them. Our data confirm a classic schema of scientific literature in which the caregiver is described as a "second victim." There is extensive literature concerning this topic.[9] So much so, in fact, that recent studies have raised the

[9] For an overview of the issue, cf. Expertise Collective Inserm (2007).

question as to whether the extant focus on this topic has had a reductive influence on the representation of the caregivers it seeks to support. Thus, leading caregivers to be viewed primarily through the prism of being a "second victim," and minimizing the procedures by which they make sense of, and give meaning to, their activity (Samitca 2004).

These processes are relevant in the context of this research: the help provided does not engage the caregiver in a positive process. The *invasion* (Samitca 2004) refers to the ever-increasing place taken by the disease in the life of the carer and how it leads them to progressively curtail their personal commitments until their life becomes a succession of responses to the endless demands imposed by the state of the patient. It shows how the caregiver's existence becomes subordinated little by little to the service of the patient, to the point where they become a *second victim*. The words of this 63-year-old Greek woman who has been looking after her sick husband for 5 years epitomizes this situation: "It's impossible to have a social life when someone needs you 24 hours a day. You can't do anything anymore! You put everything aside, you cut yourself off from everything and that inevitably has consequences on your life."

As heuristic as this idea of *invasion* may seem, it would appear to be somewhat limited for describing the transformations experienced by caregivers in these situations. We consider that *invasion* does not sufficiently take into account the states in which the caregivers do not have the time or space to accomplish other activities and in which their very existence is the object of a radical redefinition. The caregivers are eventually no longer invested in a relationship of care but in one that is essentially ancillary, in which their place, their affect, and their representations of the surrounding world are no longer *invaded* but *absorbed*. The high frequency of crying during the interviews was a significant indicator of this. At the Swedish site, Maria, wife and principal carer of Fredrik, confides, before breaking down: "I think it is quite sad that…that we won't be able to do that many things in the future, I guess that is what it is, I feel tears coming down every time I think about this" (she starts to cry). The carers who find themselves in this situation project themselves into the disease or, to put it another way, are no longer able to think outside of the disease. This is what Cecilia, a French caregiver, reports, before breaking down: "When you have someone who's got this illness (…) you get very scared that it will happen to you, so you put yourself in their place, but you also put yourself in your children's place, and I've already told them, I don't want them to take care of me, I don't want it, I want them to put me in a home, I don't want my children to have this extra burden because it's a horrible illness…" (she starts to cry). The situation is even harder for those who no longer have the means, including financially, to establish any kind of distance. This is the case for Jean-Luis, for example, whose pension hardly covers the cost of care in spite of the social security payments he receives. Many cases of this kind were recorded in the Greece sample.

In circumstances like these and after years of increasing difficulty, care (Laugier and Paperman 2008) tends to result in a patient/caregiver relationship that is thought of in terms of a burden. With care exhausted and a relationship that tends to be summarized only by its practical and restrictive aspects, the caregiver can end

up developing surprising attitudes towards the patient, where there is no longer any sign of compassion in their actions. Feelings of having "had enough," anger momentarily directed at the sick person, feelings of exasperation, and mistreatment can all manifest themselves on the part of the carer, which, in turn, may feed or be compensated by feelings of guilt.

13.9 The Idea of "Anticipatory Grief"

Anticipatory grief (Pozo 2004)[10] refers to the paradoxical situations expressed by the caregivers interviewed or recognized in them by professionals. Such situations are characterized by a painful form of adaptation to the decline of the loved one who, little by little, is retreating into the world of Alzheimer's disease. Thus, anticipatory grief is characterized by situations in which the caregiver has to accept the loss of the person that they have known and loved. The caregiver must also accept the loss of the possibility of continuing the exchanges upon which their relationship was built while at the same time still being physically close to them. The resolution of this emotional challenge is not a simple matter and can result in an attitude of rejection on the part of the carer. At the end of an interview carried out in France, off-microphone, Stephanie became particularly eloquent on this subject. For her, her mother was no longer her mother and, in her own words, she felt engaged on a real path of "mourning that has already begun." Furthermore, Stephanie admitted that she would have preferred her mother to be more physically afflicted so that her anticipatory grief had something more concrete to base itself on.

Anticipatory grief thus appears as a process of affective distancing which should help the carer in the daily pursuit of its activity. This is its paradoxical nature, since it highlights a painful dialectic between distance and proximity. Rather than being a real criterion able to transform the general pattern of care, anticipatory grief places the loved one in a tragic perspective and changes not only the nature of the link between the patient and the carer but also the motivations for providing care.

13.10 The Carer: A Care "Supervisor?"

If recourse to formal arrangements of care places the carer in the situation of being a supervisor, it does not necessarily mean the end of caring for that person. In the majority of cases studied in France and Sweden, the two roles—supervisor and caregiver—coexist. Thus, the externalization of certain tasks presents itself to these caregivers as an ad hoc means of finding responses to questions posed by the state

[10] *Deuil blanc* (translator's note).

of the patient, to guarantee their involvement. These hybrid patterns of care show the strategic place occupied by the principal informal caregiver, leading us to consider the evolution of the room they have in which to maneuver. It is in relation to this aforementioned fact, rather than to the needs of the patient, that transactions take place with other caregivers, professional or not.

These transactions concern the volume and nature of the tasks to be carried out, but also the length of care periods. These transactions, which sometimes take the form of "little arrangements," inform us about the nature of the caregivers' commitment as the disease advances and the introduction of other (formal and informal) caregivers. The setting up of these arrangements may occur only occasionally but nonetheless is very complex. The descriptions made introduce caregivers on the periphery, who intervene on the margins of care.

Often, these "little arrangements" result in conflicts, regardless of whether the placement of the patient in an institution is temporary or permanent. Thus, the arrangements are carried out early—a managing technique that was found to occur more frequently in the French and Swedish contexts than in Greece.

13.11 Transactions Between Caregivers and Professionals

Of relevance here are, on the one hand, the management efforts of the principal caregiver which consist of transmitting their "expert" perception of care to professionals and, on the other hand, the delegation of tasks which were originally and ideally the responsibility of the family. This, however, brings about its own difficulty whereby families have to recognize their specific criteria for judging the efficiency of the work carried out. This point is particularly pertinent in that the tasks are carried out in the home of the patient, thus setting up an opposition between the knowledge of laypeople and that of the experts. During our entire study period, we observed competing definitions of the care situation. These related to its objectives, its necessity, the means of putting it in place, and so forth. This means continual revision of plans concerning what has been done and what remains to be done. To take a relatively common example, although there may be a consensus on the utility of employing professional domestic help, the details about what their job would actually entail would still require further discussion. Typical questions include: "What can I ask them to do? What are the limits to be respected?" Disagreements or conflicts will shed light on differences in priority between various caregivers and the gaps between the values they defend.

The informal and professional caregivers need to communicate to coordinate their activities. They also have to engage in *justification* to attain and satisfy the common overlying principle, in this case the patient's well-being. Such *justification* highlights the contrast that was noted between expectations in the informal sector, anchored in daily experience, and what is expected in the professional sector, based on expertise. On behalf of the informal caregivers and patients, we noted reticence when envisaging the future, along with a propensity to consider placing the patient

in an institution as a terminal event marking the end of the commitment by the informal caregivers and even the end of a life. Conversely, concerning formal care, professionals employed typical trajectories to measure and estimate the necessary tasks and the evaluations to be made. The aim, in this case, was to avoid crises and make anticipatory decisions whenever possible. On the whole, we can see different perceptions of risk, implying precaution in the formal sector and case-by-case reactions in the informal sector.

13.12 Conclusions

Taking as a starting point the practices and processes engaged in by those involved in care, the analysis proposed in this study enabled us to clarify the respective commitments of patients with Alzheimer's disease and their caregivers and to shed light on the forms and evolution of their investment in care.

Regarding the patients, the aim of this study was to examine different stages of the disease. To do so, we performed interviews with the elderly people themselves, as they are the only ones able to break the silence to which they are by default confined. Thus, it was possible to analyze behavioral problems by taking into account the idea of "decline," the patients' point of view, and the space given to their discourse. In parallel, we have evaluated the position of comparison groups in a circuit of caregiving which, all too often, eventually considers the patient as a nonperson. It is likely, then, that our results and analyses may differ from research conditions in which only one stage of the disease was examined.

In reference to the caregivers, we have been able to establish profiles of providers and/or supervisors of care and criteria which influence the different patterns of help. We have also examined the distancing of caregivers from the role of caregiver and focused on gender differences that exist in the care environment. Exploring notions such as the "career of the caregiver," "invasion," and "anticipatory grief" has allowed us to describe various practices of care and outline different, more or less coercive, forms of action. Lastly, we have attempted to clarify a number of objectives that caregivers pursue and the competing definitions of care situations, not forgetting the gap between the expectations of laypeople and those of professionals and the transactions behind them.

The comparative nature of this research allowed us to perceive the dynamics of relationships between the participants and to form a contextual point of view. This enabled us to understand the sociocultural particularities of care. The comparison of empirical data from the three sites demonstrated that, in Greece, care for Alzheimer's disease fluctuates between emerging forms of medicalization and a deep-rooted trivialization which promotes a family-based ideology. Thus, women were the providers of care for elderly people within the family. In France, and to a lesser extent in Sweden, consensus is growing around the idea that the State should play an active role in the empowerment of families, and of women in particular, faced with problems linked with elderly people. Nevertheless, care remains definitively distant from

current patterns of informal help in Greece. More specifically, Sweden, confronted with the limits of the "universalist" paradigm, is questioning the preponderance of medical dependency and exploring the transactions between formal and informal help. This will help bring to light the lines of tension between cure and care.

To conclude, the focus on the methodological tool used in this research, namely, the monographs and particularly the life stories collected amongst the elderly people, comprises the originality of this research. What these stories show, first and foremost, is the presence of the other in the dynamics of accommodation which contributes to the symbolic, spatial, temporal, and material involvement of people affected by the disease in what are called situations of "vulnerability." The passage across time and space, simultaneously individual, familial, and social, which is implied by any loss of autonomy, may be synthesized by the variability of "biographical transactions," to borrow a term from Caradec (1998). Alzheimer's disease seems to constitute a privileged mediation for such synthesis because its itinerary sheds light on the problems of interdependence, autonomy, and power. The challenge taken up by these elderly people is to retrace their life's journey through the prism of dependency. They express not only the desire to confront it but remind us to what extent, in a society where definitions of loss of autonomy are expressed mostly by people exterior to the subjects themselves, the act of speaking out constitutes a vital issue.

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Chapter 14
Implementation of a Complex Improvement Program in Aged Care

Henna Hasson and Päivi Topo

14.1 Introduction

Huge improvements in the science related to developing and identifying evidence-based practices have been made during the past decades, and several such practices have been proposed to improve the health and social care of older people. However, the science behind implementing these programs with fidelity and good outcomes for patients and clients lags far behind (Fixsen et al. 2005). For example, it has been estimated that patients in the USA received only 55 % of recommended care, and the quality of the care varied by medical condition, ranging from 11 % of recommended care for alcohol dependence to 79 % for senile cataract (McGlynn et al. 2003). There is also evidence that 20–30 % of patients may get care that is not needed or that could be potentially harmful (Schuster et al. 1998). Because of this evidence-practice gap, patients are exposed to unnecessary risks, and health and social care systems to unnecessary expenditure.

Previous research indicates that implementation may be as important for the outcome as the content of the intervention (Randall et al. 2009). The process of implementing interventions can modify the intended content of the program and also exposure patterns, by preventing interventions from reaching their targeted participants in the planned manner (Griffiths 1999). Several authors have therefore

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highlighted the importance of studying implementation processes. However, such studies have been used much more in certain subjects, such as psychiatric interventions (Bond et al. 2000) and public health programs (Steckler et al. 2002). Within other areas, such as research into the care of older people, few studies have systematically evaluated implementation processes (Levenson and Morley 2007). Thus, implementation is an increasingly important issue in health and care of older people when the organizations and care givers are expected to work according to the latest research findings.

This chapter presents findings from our work on the implementation of a care continuum intervention in aged care. It aims to describe issues that are relevant for implementation of improvement programs. More specifically, we highlight the concept of implementation fidelity as well as factors that hinder and enable implementation. The intervention concerns a care continuum model for frail older people living in their own homes (Wilhelmson et al. 2011). Older people often live in their own homes instead of in institutions, even when they are frail (Hasson 2006). These individuals often receive care from many providers and are frequently admitted to hospital (Burt and McCaig 2001; Condelius et al. 2008). Thus, different types of continuum of care or integrated care programs have been developed to reduce fragmentation and improve continuity and coordination of care (Clarfield et al. 2001; Wideman 2012). These programs often contain some component aimed at integrating care and services provided by different people and organizations, such as a care coordinator.

Several continuum of care or integrated care programs have shown positive effects, for instance on older people's medication consumption, satisfaction with care, activities of daily living, and quality of life (Ouwens et al. 2005). These programs have often included components such as a care coordinator or case manager (Hallberg and Kristensson 2004), geriatric screening, i.e., needs assessment at the emergency department (Leichsenring 2004), and team work (Johansson et al. 2009). However, no systematic analysis of implementation of these programs has been conducted, and it is therefore unclear which components of these improvement initiatives are the most efficient (Ouwens et al. 2005). In addition, little knowledge is available about improving the efficiency of implementation of continuum of care programs.

14.1.1 Evaluation of Complex Interventions

Care continuum interventions often include several care providers and professions. These health service interventions are highly complex in character, especially when compared with interventions such as trials of drugs or surgical procedures (Bradley et al. 1999). They consist of several components that might act both independently and inter-dependently. This can challenge the evaluation of the program impact (Medical Research Council 2000). The experimental studies that are most often used to evaluate interventions give little information on why certain effects were or were not found. In addition, no information is gained on whether complex interventions were implemented as intended. Thus, there might be a risk in evaluating a

program that was described in a program protocol but not fully implemented in practice (Dobson and Cook 1980).

It has been recognized that, aside from outcome evaluations, it is necessary to gain insight into the "black box" of complex interventions (Hulscher et al. 2003). A process evaluation, including information about program implementation, is necessary to evaluate complex interventions (Lipsey and Cordray 2000; Fixsen et al. 2005). A study of intervention implementation process could improve the validity of intervention findings (Campbell et al. 2000; Hulscher et al. 2003; Carroll et al. 2007) and help to explain for what specific reasons an intervention succeeded or failed (Dobson and Cook 1980). For instance, studies that fail to implement a program as planned could erroneously conclude that lack of program impact was due to the content of a particular intervention if no process measures were collected (Dobson and Cook 1980). Process evaluation can also offer information about transferability of potentially effective programs to other settings (Bradley et al. 1999).

14.1.2 Implementation Fidelity

It is essential that evidence-based programs are implemented according to the program descriptions. The reason for this is that the strongest effects are found when the methods are implemented with high fidelity (McGrew and Griss 2005). Some programs did not show any effects when implemented with low fidelity. Implementation fidelity has been used as a measure of the degree to which an intervention was implemented as intended (Dusenbury et al. 2003). The idea is to compare actual delivery of a program with a standard of the program (i.e., a description of the planned program and implementation) (Rossi et al. 2004). Carroll et al. (2007) proposed *The Conceptual Framework for Implementation Fidelity* to guide evaluation of implementation fidelity. According to this, the measurement of implementation fidelity consists of subcategories—content, frequency, duration, and coverage (dose). The framework is presented in Fig. 14.1. Thus, fidelity relates to the content and dose of the intervention, i.e., whether the active ingredients of the intervention have been received by the participants as often and for as long as was planned.

The framework suggested that fidelity is influenced by four moderating factors: *participant responsiveness to a program*, *complexity of an intervention*, *facilitation strategies*, and *quality of delivery*. In our studies, we added two moderating factors to the model: *context* and *recruitment* (Hasson 2010). These have, in previous studies, been shown to be important determinants of successful change and implementation. Context has been defined as surrounding social systems, such as structures and cultures of organizations and groups, inter-organizational linkages, and historical and concurrent events (Lipsey 1996; Lipsey and Cordray 2000). Recruitment refers to procedures that were used to attract program participants (Baranowski and Stables 2000; Steckler et al. 2002) and includes areas such as potential participants' reasons for nonparticipation, subgroups that were less likely to participate, and consistency of recruitment procedures. Intervention complexity refers to description of

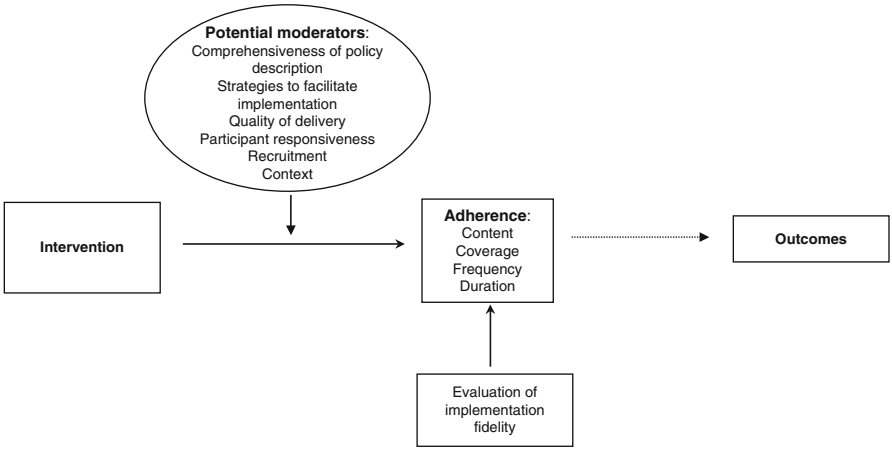

Fig. 14.1 The modified version of the *Conceptual Framework for Implementation Fidelity* (originally from Carroll et al. 2007 and Hasson 2010)

the intervention and the nature of the intervention. It has been suggested that interventions that are described in detail are more likely to be implemented with high fidelity than ones with vague descriptions. In a similar manner, complex interventions are more difficult to implement with high fidelity than simple interventions (Greenhalgh et al. 2004). Facilitation strategies, such as provision of guidelines, training, and performance feedback, may be used to increase implementation fidelity. The framework suggests that facilitation is highly dependent on the complexity of the intervention, implying that more facilitation does not necessarily lead to better implementation results. Quality of delivery has been defined as "the extent to which a provider approaches a theoretical ideal in terms of delivering program content" (Dusenbury et al. 2003). Participant responsiveness refers to both individuals receiving the intervention and those responsible for delivering it. Higher levels of enthusiasm among participants and staff are assumed to lead to higher fidelity. Although the importance of fidelity measurement has been highlighted by several authors, there have been few systematic and longitudinal studies evaluating different aspects of implementation fidelity. Some of the results presented in this chapter have been previously published in more detail (see, for example, Dunér et al. 2011; Hasson et al. 2012; Berglund et al. 2013).

14.2 The Intervention Case

The continuum of care was a systematization of collaboration between a nurse with geriatric expertise situated in the emergency department (ED), the hospital ward staff, and a multi-professional team with a case manager (CM) in the community. The multi-professional team included a nurse (the CM), a qualified social worker, an

Table 14.1 The intervention components

At the ED, a nurse with geriatric expertise makes an assessment of the older patient's needs for rehabilitation, nursing, and geriatric care
The geriatric assessment is transferred from the ED to the hospital ward, for participants who are admitted to a ward
The nurse with geriatric expertise informs the community team that the patient has visited the ED, and whether he/she was transferred to a hospital ward or returned home
The geriatric assessment is sent to the case manager and the multi-professional team in the community
For participants who are admitted to the hospital ward:
The community-based case manager visits participants in the ward
The case manager contacts the nurse responsible for the patient on the ward to get information about the estimated length of stay
For participants discharged from the ward:
The nurse on the ward who is responsible for the patient contacts the case manager before discharge
Discharge planning is done by collaboration between the case manager, a qualified social worker, the patient, the responsible nurse on the ward, and the physician in charge of the ward
Participants coming home from emergency care or from a ward:
The case manager contacts participants returning home after visiting the emergency department and offers care planning
The case manager initiates support for patients' relatives if necessary
The case manager and the multi-professional team make a care plan a couple of days after discharge from the hospital ward. Care planning is done at the older person's own home
The care plan is based on the results in the geriatric assessment made at the emergency department
All planning is done in consultation with the patient
The team informs other professionals and care providers, such as home help services and home nursing care, of the care plan
The case manager follows up the care plan within a week, via telephone or home visit, to ensure that everything is working and no new problems have arisen
The case manager has telephone contact with participants once a month, except in cases where more frequent contact is needed
The participants are advised that the case manager is available for questions, problem-solving, and assistance during office hours
The patient's general practitioner is informed by letter that the individual is participating in the research project

occupational therapist, and a physiotherapist. The theoretical framework was that a care continuum creates networks of resources and services over time and between different healthcare providers, particularly between health and social care. The idea was to strengthen the self-reliance of the older person and their relatives. Effective components were expected to be a geriatric assessment in the ED, a community multi-professional team with a case manager, and a care plan made in the older person's home instead of in the hospital ward. The idea was to involve the older person in the decision making regarding their care planning and rehabilitation. The study design was a randomized controlled study with a total of 161 participants divided into intervention and control group. The intervention components are presented in Table 14.1. A more thorough presentation of the intervention and the conventional care has been published previously (Hasson 2010; Wilhelmson et al. 2011).

A case study method was used to investigate the implementation processes of the intervention. Longitudinal analysis (years 2008–2010), using both quantitative and qualitative methods, was used. Observations of work practices, repeated interviews with key stakeholders, questionnaire surveys to the intervention participants, and document analysis were used.

14.3 Results and Discussion

14.3.1 Implementation Fidelity

We found from the observations and interviews that, in general, the level of the fidelity was high (i.e., overall, the intervention was conducted in accordance with the program protocol). A total of 16 of the 18 intervention activities were always or most often delivered according to the program description. Below we discuss, first, the type of adaptations that were made and then, the factors that resulted in high fidelity and local adaptations.

Nonadherence consisted of intervention components that were not delivered, modified, and added to the original plan. This illustrates how fidelity does not only deal with intervention components that were not delivered but also with components that were added to the program by staff. This is an area that has not been highlighted in previous studies. One consequence is that this might challenge the measurement of implementation fidelity since most of the measurement instruments concentrate on performance of predefined activities and do not ask participants to report any new intervention components. We suggest that all measurements of implementation fidelity, such as fidelity protocols, should also include categories for additional components. However, our analysis showed that staff did not report additional activities during the interviews. These were only captured during observations. Therefore, it is recommended that observations are used to measure adherence and added components. Clearly, more research is needed to understand the concept of added intervention activities, and on the details of how to capture these in process evaluations.

When dealing with implementation fidelity it is also important to reflect on the desired level of fidelity versus possibilities for local adaptations. As mentioned earlier, implementation with high fidelity is often related to better patient outcomes in clinical studies. However, research from the field of social sciences has also shown that allowing local adaptations may improve outcomes and program sustainability (Czarniawska-Joerges and Sevón 1996). This perspective is in line with theories on organizational change, showing that change is more likely to be sustained when the intervention fits the needs and goals of staff members and organizations. Thus, the balance between adherence to evidence-based programs and local adaptations is complex. More research is needed, including detailed analysis of different types of adaptations and immediate and long-term impact of these on participants'

health and well-being. That would offer guidance to researchers and practitioners in making local adaptations to predefined programs.

Fixsen et al. (2005) highlighted that understanding of the principles of intervention core components may allow for flexibility in form without sacrificing the potential benefits associated with each component. With this approach, staff members are not expected to follow process protocols exactly, but rather work according to their own judgments of what fits with the client characteristics and context and the program theory (Mowbray et al. 2003). It has also been suggested that decisions about any program changes should be made by practitioners who know the local conditions, together with administrators who understand the theory behind the program (Fixsen et al. 2005). In addition, it has been suggested that different hierarchical levels in an organization should be involved, since they have different levels of decision-making power, as well as different motivations for decisions. For instance, one study found that organizational-level adaptations were made by senior managers in order to create alignment with existing policy, and to guarantee cost benefits. At the unit level, adaptations were made to balance the components in the intervention with the business goals and productivity of the unit and employee preferences (von Thiele and Hasson 2013). We suggest that staff, managers at different organizational levels, and program administrators could together develop their understanding about the program logic. Program logic (often also called program theory) includes a description of the actual program and its theoretical basis, purpose, core activities, and expected outcomes. Work with program logic would increase participants' knowledge about the practical work activities and also the underlying principles of the intervention. Such work often starts with identifying core intervention components. These are the aspects of an intervention that are crucial for achieving the expected outcomes. Work with program logic also involves illuminating the logical steps between these components, immediate and intermediate outcomes and the impact (Hasson 2010). It is suggested that exercises with program logic should be done before the intervention is initiated to prepare all stakeholders for the actual implementation (von Thiele and Hasson 2013). This in turn raises the practical question of how detailed clinical guidelines or work descriptions should be, so that both the principles of a program and practical work instructions can be illustrated. We return to this question below when analyzing how program complexity and level of detail in work descriptions affected the fidelity of the care continuum model.

14.3.2 Moderating Factors

When analyzing factors affecting fidelity and nonadherence, we found that changes in fidelity were caused in a complex, interrelated fashion by all the moderating factors in *The Conceptual Framework for Implementation Fidelity*. We found that staff enthusiasm for the project (responsiveness) was high, and this was the reason for adding components to the intervention. Staff had a desire to improve the program effects on older people's health and thus they added components that they thought

would be beneficial. This is in line with Fraser et al. (2009), suggesting that a desire to improve program results can be a reason for local intervention adaptations. We also found that some contextual factors such as merging services with concurrent projects and additional resources enabled the staff to add components. Thus, contextual factors enabled additional components, but staff responsiveness determined whether they were actually added. Staff with lower enthusiasm would probably not have added the components even though contextual factors made it possible. Contextual factors can therefore be considered as necessary for implementation, but cannot on their own guarantee successful implementation.

Other contextual factors, such as increased workloads, made staff remove the added components later on in the project, to be able to focus on the original components. This is a typical situation in organizational intervention research where interventions are not conducted in a vacuum. Instead, staff strove to strike a balance between resources and workloads on the one hand and their willingness to deliver high quality care on the other hand. Fixsen et al. (2005) suggested that high fidelity is best achieved when implementation is well supported by strong organizational structures and cultures. This is certainly valid, but difficult to achieve in practice when dealing with organizational interventions during a longer time period. This project had strong leadership support and the content of the intervention was developed in collaboration with the participating groups to develop a program that would suit the local context (Wilhelmson et al. 2011). However, organizations change managers and reorganize their operations, both of which make it difficult to plan longitudinal interventions in advance. This further emphasized the importance of longitudinal, systematic analysis of implementation and potential changes in the relevant organizations.

We also found that the older people's preferences were a reason for not delivering intervention components as planned in the intervention protocol. For instance, the case manager was supposed to contact all participants at least once a month to check their status. However, some participants wanted to contact the case manager by themselves and as often as they wished. Previous studies have shown that parts of an intervention that are not in line with recipients' wishes are most often not delivered (Martens et al. 2006), emphasizing the importance of paying attention to older people's preferences, and balancing those with program fidelity. These results illustrate how some intervention components and the underlying principles of these components can be contradictory. One of the principles of the intervention was that all activities should be based on the preferences of the older people concerned. However, the case manager had detailed work instructions such as contacting the participants to a certain time schedule. In this example, the principle of the intervention (i.e., older people's preferences) was naturally a stronger argument when making decisions about whether to adhere to the protocol or adapt.

It has been suggested that intervention complexity and facilitation influence fidelity. Staff in our study experienced the intervention as a complex program, the description of the intervention as vague, and the initial facilitation as limited. However, this was not perceived as negative by all participants. While some described the lack of clear descriptions as frustrating and hindering, others experienced it as a positive, because it allowed them to interpret the intervention. The social services staff in

particular, who had considerable experience in working on similar projects, reported that they took a more active role and enjoyed the freedom to act according to their own judgment. Our interpretation is that the complexity and lack of initial facilitation did not affect fidelity, which is contradictory to previous studies suggesting that simple interventions and those with detailed descriptions are more likely to be implemented with high fidelity (Carroll et al. 2007). In this study, the staff members were highly enthusiastic about the intervention, which may have functioned as a driving force for them to solve complicated practical issues and take a more active role in the implementation. Some studies have reported staff to be more engaged, motivated, and effective when they feel they are exercising their judgment and expertise (Glisson and Hemmelgarn 1998; Henry et al. 1993).

Our findings emphasize the interrelationship that the moderating factors can have with each other and fidelity. These factors interact with each other and the effect of one factor on fidelity might be moderated by another factor. For instance, previous staff experience of similar projects affected their responsiveness to this project to a considerable extent, which in turn influenced their preferred level of detail of work descriptions and facilitation strategies. Many contextual factors also hindered and facilitated the work of the project staff, while the impact of these factors on fidelity seemed to be modified by other factors, such as staff responsiveness. It has been suggested that implementation components, such as training, need to be standardized, but also flexibly adapted to different provider levels of experience (Borrelli 2011). In line with that approach, our findings suggest that it is important for those delivering an intervention to consider individual and organizational differences in prior experiences and responsiveness to the intervention, especially when developing work descriptions and planning facilitation activities. Fixsen et al. (2005) suggested that the interactive moderating factors compensate for one another, so that a weakness in one component, such as lack of facilitation, can be overcome by strengths in others, such as strong leadership support. It is suggested that future research should focus on investigating the interrelationships between different moderating factors and examining the relative impact of these factors on each other and on fidelity.

14.3.3 Fundamental Conditions for Implementation Fidelity: Willingness and Ability

Based on the results of our study, it seems that staff willingness to deliver the program with high fidelity and participants' willingness to receive the components were the fundamental conditions for implementation. Factors of particular importance for fidelity were staff and participants' responsiveness to the intervention, and the enabling and hindering contextual factors. Implementation fidelity was shaped by staff commitment to the intervention program, as well as their ability to perform its content within the resources at hand. Staff who were highly responsive were also willing to overcome potential obstacles, such as contextual factors. In the interviews, it also became evident that the interviewees' commitment to the intervention

was closely connected to its potential benefits (Dunér et al. 2011). Among senior managers, the commitment to the model primarily had to do with its economic effectiveness. At the operational level, the commitment was closely linked to the ideology of care. The operational staff noted occasions when the needs of older people had been neglected both at the hospital and in the community, and welcomed the possibility of working in an integrated, instead of fragmented, manner. This illustrates how staff and managers might have different reasons for being willing to implement improvement interventions. Having knowledge of the underlying perceived benefits among different stakeholder groups is therefore crucial for successful and sustained implementation.

One important enabling factor was management support. According to the employees, the role of senior management in the organizations emerged as crucial to their ability to introduce and implement the intervention. Managers' support for the model had both a symbolic and an actual value, and was therefore necessary, although it was affected by environmental factors, such as new, competing, ideas and trends. In the middle phases of the project, some skepticism among the management in the community became evident. The intervention had been planned more by the senior management in the organization, and the managers directly responsible for the "ordinary" nurses, social workers, and rehabilitation staff members were not convinced of its benefits. These managers were key players for full implementation, and they stated that an unequivocal decision needed to be taken at the top of the organization as to whether they should promote the intervention.

In addition, support from colleagues and "unlearning" of traditional ways of working were important. Initially, the representatives from the community reported that some of their colleagues were hesitant about adopting the new model, since it involved changes to well-established professional roles and working methods. The model gave the case manager extended authority that was normally delegated to home nurses. In addition, the social workers and their manager were skeptical about the model since some of the social workers' normal responsibilities were now devolved to the case manager. The rehabilitation staff in the team initially did not assess the rehabilitation needs of the older people as intended, in order to avoid potential conflict with their colleagues.

14.3.4 Intervention Outcomes on Older People's Satisfaction

We also investigated how the participants (i.e., older people) perceived the intervention services (Berglund et al. 2013). In this study, the intervention group was compared to those older people receiving the usual care. Our findings showed that the older people receiving the intervention perceived a higher quality of care than those receiving the usual care at 3-month follow-up points. The items measured their perceived value of the care-planning meeting, opportunities to participate in the meetings, responsiveness of the services planned including the home help service, home nursing care and rehabilitation, training, assistive technology, and/or home modification in relation to their needs. They also rated significantly higher their

knowledge of whom to contact if they needed any help. This implies that the combination of the intervention services aiming to create a continuum of care had beneficial effects on older people's views of their quality of care.

14.4 Conclusions

This chapter has highlighted the difficult balance between adhering to a predefined program and allowing local adaptations. We found high implementation fidelity (i.e., in practice, the program was implemented as it was described to a high degree). However, we also saw that staff needed to constantly reflect and manage the changing organizational circumstances, together with the wishes and preferences of participants (i.e., older people). This sometimes led to changes in the intervention activities, although the overall fidelity was high. An important factor in this complex situation was the commitment of staff to the program. Staff considered the intervention to have real potential to improve the well-being of older people, which motivated them. One of the clearest results from the study was the complex interplay between the different moderating factors. These factors, such as prior experiences of similar projects, managers' attitudes and actions, and facilitation offered for the implementation, interacted with each other and together affected the fidelity. Thus, the effect of one factor on fidelity was moderated by another. This implies that factors potentially important in implementation compensate for one another, so that a weakness in one component can be overcome by strengths in others. This means that implementation processes will be different in different organizations, and at different time points in the same organization. This makes it challenging to give general guidance on implementation. We have suggested that stakeholder groups, such as managers, staff, and administrators, could use the theory behind the program as guidance in understanding the underlying principles of an intervention, and also in preparation for the actual implementation.

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Chapter 15
Can Executive Functions Be Trained in Healthy Older Adults and in Older Adults with Mild Cognitive Impairment?

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15.1 What Are Executive Functions?

Executive functions (EF) are crucial for learning new information and skills. These functions refer to goal-directed, flexible use of cognitive abilities, i.e., sustaining, dividing and shifting attention according to task demands, inhibiting inappropriate responses in tasks that require attentional control (often measured by the classic *Stroop* task, where the name of the color of the ink in color incompatible words are named, e.g., the word "green" is printed in blue ink instead of green ink), initiating appropriate/adaptive behaviors, self-monitoring (i.e., the ability to assess one's own cognitive performance correctly), and solving problems. They seem to represent a cluster of closely related but separable cognitive processes that to a great extent rely on prefrontal brain regions (Miyake et al. 2000). There are a number of theories on the organization of EF, and the concept is far from clear-cut, but common across most EF models is the thought that EF allow us to behave in a goal-directed way (Banich 2009). One of the most well-known models of EF is that of Miyake et al. (2000), and it postulates that there are three major EF that are strongly interrelated but separable, namely (1) *working memory* (*WM*) *updating* (i.e., what we are focusing on at the moment, can be verbal, numerical, visuospatial information, for example trying to keep somebody's name or phone number actively in mind), (2) *inhibition* of task irrelevant responses (e.g., Stroop task that requires deliberate suppression of conflicting color words when naming ink color), and (3) *shifting* between tasks and mental sets (e.g., having to classify number as even or odd or letters as vowels or consonants in series of number-letter pairs, depending on where the number-letter pair is presented on a computer screen). This tripartite division will be used in the present chapter, when presenting results from EF training studies.

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15.2 Trainability of EF

There are numerous studies on the training of EF in young adults, especially when it comes to working memory (WM) training (Klingberg 2010; Morrison and Chein 2011). As opposed to *strategy training* where effective approaches to e.g., retrieval from WM are taught, so called *core training* of WM has become a popular training method in recent studies (Morrison and Chein 2011). Core training involves repetition of demanding WM tasks, for instance updating of running memory spans (Shipstead et al. 2012), that are thought to tap more general WM mechanisms. In running memory span tasks, sequences of items (e.g., letters) are presented and when a sequence ends, the task is to recall a given number of the last items presented (Broadway and Engle 2010). The underlying logic is that this type of core training of WM should broaden the attentional capacity needed for a number of tasks. In other words, it is predicted that WM training gains should generalize to both closely and not so closely related tasks, i.e., show near and far *transfer* to, firstly, other working memory tasks, and secondly, to other higher level cognitive functions, such as fluid intelligence (Shipstead et al. 2010). Another way of looking at EF training, especially when planning treatment attempts for populations with executive dysfunctions, is seeing it as either *restorative* or *compensatory* (Elias and Treland 2000). While restorative EF training aims at improving EF (cf. with core training), instead of merely compensating for EF decline, the compensatory approach focuses on compensatory strategies in order to help the client to function despite executive dysfunction (cf. with strategy training). When it comes to planning interventions for clinical populations, the expected course of an illness needs to be taken into consideration, i.e., in some conditions the rehabilitation goal can be restorative in an earlier phase of the illness, and compensatory at a later stage (Elias and Treland 2000).

The promising results from WM training studies have resulted in many commercial, computerized brain training programs, targeting especially older persons and children (Melby-Lervåg and Hulme 2012). A recent meta-analysis (Melby-Lervåg and Hulme 2012) as well as recent reviews (Buitenweg et al. 2012; Morrison and Chein 2011; Rabipour and Raz 2012; Shipstead et al. 2010, 2012) have suggested that the training effects are not as robust and consistent as previously thought, due to methodological shortcomings of EF training studies, and the improvements do not persist long term. On the other hand, results from a recent study that was better controlled for (including an active control group), showed both near and far transfer of working memory training (Brehmer et al. 2012). Further studies are needed to find out to what extent EF can be trained. In the following, EF and EF training studies in old age will be reviewed.

15.3 Executive Functions in Old Age

A number of studies have shown that cognitive functions are somewhat compromised during aging (Bäckman et al. 2002; Nyberg et al. 1996). Especially reaction time, cognitive processing speed, and executive functioning have been found to

decline with age, whereas vocabulary, skills, and knowledge are maintained or even enhanced in late adulthood (Compton et al. 2000; Gottsdanker 1982; Salthouse 1993, 2000; Zelazo et al. 2004). Additionally, a number of studies have shown declines in episodic, short-term memory, and working memory functions in normal aging (Nilsson 2003; Nyberg et al. 2003; Park et al. 2002; Ratcliff et al. 2004; Verhaeghen and Salthouse 1997). According to Park et al. (2002), the decline in e.g., speed of processing and working memory starts at an early age, namely in the 20s, but is probably not noticeable before the 40s and 50s (in demanding tasks), and does not start to affect everyday functioning before the 80s and 90s.

Substantial age-related changes in executive abilities, with improvement during childhood and subsequent decline in older age, have been observed in previous studies employing various kinds of experiments (Bedard et al. 2002; Cepeda et al. 2001; Kray et al. 2004, 2008; Verhaegen et al. 1993; Williams et al. 1999). More specifically, decline in older age has been found in tasks measuring inhibitory control (i.e., decline in the ability to withhold incorrect responses) (Sweeney et al. 2001; Williams et al. 1999), ability to flexibly switch between two different tasks (Cepeda et al. 2001), ability to select between task sets (Kray et al. 2004), and in working memory tasks (Park et al. 2002).

15.4 EF Training in Old Age

As EF decline in normal aging, training of these functions could potentially help older persons maintain an active and independent lifestyle, which is important for the quality of life. However, this type of support or training, from which healthy older individuals could benefit, is seldom provided for them (Elias and Treland 2000), as EF decline is often seen as a "normal" phenomenon of aging.

There is some evidence showing that children, younger adults, as well as older adults, can benefit from executive training and even show transfer to untrained tasks (Bherer et al. 2005; Dowsett and Livesey 2000; Klingberg et al. 2005). The effects of executive training and the generalization of these effects are, however, far from clear (Owen et al. 2010). Brain training studies have shown mixed results (Rabipour and Raz 2012). While some studies show that training can improve cognitive functions that are closely related to the intervention (e.g., working memory training leading to improved performance on another working memory task, i.e., *near transfer*), at least some findings suggest that training may generalize to other cognitive domains (e.g., working memory training leading to improvement on a task measuring fluid intelligence, i.e., *far transfer*).

Studies on memory training have suggested that age-related processing deficits, including EF problems, may prevent older persons from using metacognitive strategies (i.e., potentially useful learning strategies) as efficiently as young persons (Jones et al. 2006), and in this way also affect their memory performance. Also, EF and memory functions seem to interplay in other ways, as research findings have shown that certain EF and memory functions decline at the same time in healthy aging (Bisiacchi et al. 2008). As EF and memory are related functions, it would be of interest

to find out if more general, process-based EF training could optimize cognitive performance in older persons also when it comes to learning new information.

Although it is widely thought that cognitive activity enhances or maintains cognition in late adulthood, relatively few EF training studies have been conducted in healthy older persons (compared to the amount conducted in healthy young adults), and the training paradigms that have produced the broadest gains in terms of transfer effects in young individuals have not been studied in healthy older adults (Morrison and Chein 2011). Recently, however, an increasing number of training studies in healthy late adulthood have been conducted, including training of EF, most of which have been WM training studies (Brehmer et al. 2011, 2012; Buschkuehl et al. 2008; Cassavaugh and Kramer 2009; Dahlin et al. 2008; Nouchi et al. 2012; Uchida and Kawashima 2008; Zinke et al. 2013). Especially the WM training study by Brehmer et al. (2011) is of interest, as it to the author's knowledge is the first EF training study in normal aging that has used an active control group where subjects performed a similar task as the experimental group, with the exception that it was unadaptive, i.e., task difficulty was fixed at a low level. Despite the very well controlled for assessment of training gains, Brehmer et al. (2011) found transfer effects after 5 weeks of WM training. More specifically, transfer was found to other non-trained WM tasks and to a test of sustained attention, as well as an episodic memory task in the training group, compared with the active control group. In another recent, also well controlled for study, where WM training effects in younger and older adults were studied, Brehmer et al. (2012) found that training and transfer gains were greater for younger than for older participants in one of the WM tasks (Span Board task, where the test leader points to a sequence of blocks and the subject then points to the same blocks in the same order or in the reverse order), but similar in another WM task (Digit Span, where a lists of numbers are read out loud and the subject is then asked to recall the items in forward or backward order) and a task measuring sustained attention. In addition, both older and younger adults reported less memory complaints after WM training compared to the active control groups, and importantly, the observed training gains and transfer effects were maintained across a 3-month time interval (Brehmer et al. 2012). Also, Richmond et al. (2011) conducted a WM training study where healthy older adults were trained with complex WM tasks (where subjects had to do two tasks intermittently, e.g., make a series of word/nonword decisions and intermittently encode a sequence of letters that should be recalled), and they found significant transfer effects to verbal learning, as well as to self-reported "everyday attention" ratings. Taken together, these results suggest flexibility regarding WM functioning, which is encouraging, as WM processes are thought to decline with age (Park et al. 2002). On the other hand, previous WM training studies in healthy older adults that have not included an active control group have usually reported reduced or nonexistent transfer effects (Borella et al. 2010; Buschkuehl et al. 2008; Dahlin et al. 2008; Li et al. 2008). Therefore, future studies with both an active and a passive control group would be valuable in order to clarify the transfer effects of WM (and other types of EF) training.

In addition to WM, effortful *inhibition*, i.e., the ability to deliberately suppress/ignore stimuli that are irrelevant to the task at hand (Miyake et al. 2000), has been

found to decline with age (Andrés et al. 2008). Inhibition can be seen as a subcomponent of attentional control (Jurado and Roselli 2007). As compared to WM, relatively few studies tapping training of inhibition or other aspects of attentional control have been conducted with normal older subjects (Bherer et al. 2006; Erickson et al. 2007; Mozolic et al. 2011). Relating closely to inhibition, studies on dual-task training that call for attentional control have indicated that healthy older adults can benefit from this type of training, both in terms of training gains and transfer gains (Bherer et al. 2005, 2006; Erickson et al. 2007). Mozolic et al. (2011) studied the effects of attention training in healthy older individuals compared to an active control group. They found that repetitive, adaptive practice, where the trained subjects had to focus on relevant tasks and at the same time ignore irrelevant, distracting stimuli, improved healthy older adults' ability to ignore cross-modal stimuli (visual task calling for suppression of auditory distractors), and the training also showed transfer effects to other cognitive tasks, such as dual-task completion. In sum, existing studies on training of attentional control suggest that older adults can benefit from this type of intervention.

Set-shifting (or task-switching) requires switching between tasks or mental sets (Miyake et al. 2000), often measured by the *number-letter task*, where one has to shift between having to classify numbers as even or odd or letters as vowels or consonants depending on where number-letter pairs are presented on a computer screen. Set-shifting and inhibition are closely related, both of which require cognitive control and have been found to at least partly recruit the same brain areas in the frontal lobe (Derrfuss et al. 2005; Shallice et al. 2008). Set-shifting training and its transfer effects have been very scarcely studied (Karbach and Kray 2009; Minear and Shah 2008). Karbach and Kray (2009) studied set-shifting training in children, young adults, and healthy older adults. The training regime included a set-shifting task where subjects alternately had to decide whether the pictures showed planes or cars or whether one or two planes/cars were presented. Near transfer effects in reaction times to another structurally similar set-shifting task (where subjects had to alternate between deciding whether a picture showed a fruit or a vegetable or whether a picture was small or large) were found in all age groups, but especially in children and healthy older adults. In other words, set-shifting training improved the subjects' performance on another set-shifting task in terms of reduced mixing cost defined by Karbach and Kray (2009) as the difference in mean performance between the shifting task and a non-shifting task). In addition to near transfer, far transfer to inhibition, verbal and spatial WM and even fluid intelligence (as measured by a figural/reasoning/letter series task and Raven's Standard Progressive Matrices) were found in all age groups. Minear and Shah (2008) studied set-shifting training in young adults, and they found near transfer effects (far transfer was not measured). Additionally, playing online cognitive training games that require task-switching, as well as selecting and integrating information and manipulating WM representations, has been found to affect inhibition and inductive reasoning in healthy older adults, as compared to control subjects answering quiz questions about documentaries online (Van Muijden et al. 2012).

Another interesting phenomenon that relates to set-shifting (and inhibition) training is bilingualism. Bilingual persons have been found to have an advantage in executive tasks, especially tasks measuring set-shifting, inhibition, and WM (Adesope et al. 2010), probably due to the fact that the managing of two languages requires additional executive resources. It is also of interest to mention that recent studies have suggested that bilingualism may create a cognitive reserve that may protect against cognitive decline and even postpone symptoms of dementia (Bialystok et al. 2007; Craik et al. 2010).

As set-shifting training studies are scarce, future studies are needed to find out to what extent set-shifting training can transfer to other tasks, and how consistent the possible effects are. This would be of interest, as set-shifting abilities are known to decline with age (Zelazo et al. 2004), and associations between poorer set-shifting performance have been related to age-related white matter reductions in frontoparietal brain areas (Kennedy and Raz 2009).

15.5 EF Training in MCI

Mild cognitive impairment (MCI) has become an important research topic, as patients with this condition have been shown to be at risk of developing Alzheimer's disease (AD) or other neurodegenerative diseases (Collie and Maruff 2000; Petersen 2004; Petersen et al. 2001). There is heterogeneity concerning the MCI criteria, but generally MCI refers to persons who do not fulfil the criteria for AD or dementia, but who show some form of cognitive decline (Palmer et al. 2003). Of particular interest is amnestic MCI that refers to subjects with isolated episodic memory impairment (Collie and Maruff 2000; Petersen 2004; Petersen et al. 1999, 2001). Amnestic MCI is the form that most often leads to AD (Petersen and Morris 2003) and thus often represents the prodromal phase of AD encompassing amyloid deposition in cortical areas (Nordberg et al. 2013). Although episodic memory impairment is the key deficit in MCI (Collie and Maruff 2000), also preclinical deficits in executive functioning have been found in these patients (Collie et al. 2002; Davie et al. 2004).

In MCI, most cognitive intervention programs have targeted episodic memory, although some have also involved EF (Simon et al. 2012). Executive functions could be an important target to study in MCI, as EF have been shown to interplay with memory functions and an improvement of EF could potentially also have an impact on the ability to encode episodic memory traces (Raganath et al. 2005). Recent neuroimaging findings have indicated that the role of EF as a compensatory mechanism in MCI could be of importance, as Clément et al. (2013) found that MCI patients with relatively mild cognitive symptoms showed large areas of hyperactivation during EF tasks. This hyperactivation, in turn, suggested a successful compensation mechanism, i.e., patients with MCI in an early phase were able to benefit from neural reorganization. It should also be noted that although the entorhinal cortex and hippocampus in the medial temporal lobe (MTL) are the brain areas first affected in those MCI patients that will convert to AD (De Toledo-Morrell et al. 2004; Dickerson et al. 2001; Karas et al. 2004; Pennanen et al. 2005), there are several reciprocal

anatomical connections between MTL structures and the prefrontal cortex (that is a critical area for EF) (Corkin 2001). Additionally, despite their memory problems, MCI patients have preserved abilities to learn new information (Grönholm-Nyman et al. 2010), and therefore attempts at training EF, a better preserved domain of cognition in MCI (Collie and Maruff 2000), could be potentially useful in strengthening e.g., the learning ability of these patients. Also, MCI patients are by no means immune to the age-related decline of EF, and therefore possible training-related EF gains in healthy older adults could benefit MCI patients as well.

15.6 Summary

Most of the EF training studies have focused on the trainability of working memory, and these studies have shown either near or far transfer effects, or both, after WM training (Klingberg 2010; Melby-Lervåg and Hulme 2012; Morrison and Chein 2011; Shipstead et al. 2010, 2012). The promising results from WM training studies have resulted in many commercial, computerized brain training programs, targeting especially older persons and children (Melby-Lervåg and Hulme 2012). A recent meta-analysis (Melby-Lervåg and Hulme 2012) as well as recent reviews (Buitenweg et al. 2012; Morrison and Chein 2011; Shipstead et al. 2010, 2012) have, however, suggested that the training effects are not robust and consistent, and the improvements do not persist long term. On the other hand, results from a recent study that was better controlled for (active control group/adaptive training) showed both near and far transfer of working memory training for both younger and older adults (Brehmer et al. 2012). More studies that are better controlled for are clearly needed in order to find out to what extent EF training can benefit the quality of healthy older persons' life and to support cognition in late adulthood. Firstly, as pointed out by Shipstead et al. (2012), training periods should be long enough (approximately 20 sessions lasting 30–60 min) and the training regime should be adaptive, i.e., task difficulty should increase as the subject's performance improves. Secondly, the control groups should be active in order to avoid general effects that taking part in an experiment may cause. Thirdly, possible transfer gains should be assessed with multiple tasks (at least two tasks per domain). Additionally, follow-ups should be conducted to find out how permanent the transfer effects are.

Previous cognitive training studies in normal aging have mainly focused on improving episodic memory using different mnemonic strategies, such as rehearsal of items, forming associations between items, or categorizing items (Gross et al. 2012; Stigsdotter Neely 2000). The same holds true for training studies in MCI (Simon et al. 2012). The limitation of mnemonic strategies is that they do not generalize to other types of tasks. Nevertheless, a large number of studies have reported positive effects of memory strategy training, both in healthy older adults and adults with MCI (Gross et al. 2012; Simon et al. 2012). The following probably also holds true for EF training, as pointed out by Stigsdotter Neely (2000, p. 77) in relation to memory training in normal aging:

To ensure positive benefits from memory intervention, a good piece of advice is to guide training after the notion of task specificity—focusing the training specifically on those particular tasks, skills, and behaviors that are of primary interest to the learner.

In an aging population, cognitive interventions that could improve the everyday functioning of older people are essential. Therefore it is of great importance that different types of training programs are investigated in the future, in order to evaluate their effectiveness.

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Part IV
How to Ensure Healthy and Active Aging Through Policy and Practice

Chapter 16
A Master's Degree in One's Fifties: A Way to Stay Active Beyond the Retirement Age

Ulpukka Isopahkala-Bouret

Since the 1990s the European Union has strongly supported policies of active ageing, and the European Commission designated the year 2012 as 'European Year on Active Ageing and Solidarity between the Generations'. The policy discourse of active ageing has moved from a narrow economistic and productivist approach, which has mainly focused on the extension of involvement in the labour market beyond retirement age, toward a broader understanding of older people as active participants in society (Walker and Maltby 2012). Active ageing, then, refers to continuous participation in all kinds of societal activities, including paid and non-paid work, family affairs, as well as cultural and spiritual activities (WHO 2002). Active involvement through different kinds of activities reduces the risk of social exclusion and isolation (Ehlers et al. 2011) and supports health and well-being at old age.

Education and lifelong learning assist active ageing by prolonging working careers and by helping in the transition to retirement (Davey 2002). Once retired, educational attainment keeps older people occupied in leisure time, updates their skills, and encourages further participation in society. Participation in courses during old age is seen as a way to maintain physical and mental activity and to decrease loneliness while increasing cultural knowledge (Ojala 2010). In promoting active ageing maintaining mental capacity is seen as important as physical activity (Walker and Maltby 2012). However, educational research and adult educators have not been strongly involved in the planning and implementation of the policies of active ageing.

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This chapter[1] explores the relationship between adult graduation and active ageing. More specifically, the aim is to understand how degree-orientated university studies in midlife impact the future retirement prospects of adult graduates. The data consists of interviews with graduates who have acquired a master's degree in their fifties. The analysis will show that adults who have participated in an extensive educational activity and upgraded their educational level at mid-age are planning to stay active at old age. They anticipate being involved with various activities in which they can utilize the knowledge, skills, and social position provided by the academic education.

16.1 University Studies in Midlife

There have been earlier studies on access, motives, study experiences, and outcomes of adult learning in the context of higher education (e.g. Phillipson 2010; Rinne et al. 2008; Moore 2003; Waller 2010; Reay 2003; Pascall and Cox 1993; Edwards 1993; Merrill 1993; Marshall 2000; Britton and Baxter 1999). Most of these studies have not focused exclusively on older adults (see however Davey 2002; Jamieson 2007; Creech et al. 2010), or then the focus has been on older adults in the university of third age (Ojala 2010; Wilinska 2012; Muhonen 2013). There have been also recent studies on ageing at work and on learning and development of older employees (some examples of Finnish studies, see Ruoholinna 2009; Irni 2010; Paloniemi 2004). However, there has been only a little research engagement to date focusing simultaneously on higher education graduates and future retirement prospects.

This study focuses on those older university graduates who are still actively participating in working life. For them university studies are not mainly a hobbyist activity. Earlier studies have shown that a majority of those people who enter university at older age, especially those who are doing master's level studies, want to acquire new knowledge and/or qualification to improve job performance and their future career prospects (Davey 2002). A large majority of those over 50 still see the recognized qualification as a very important reason for enrolling to higher education studies (Jamieson 2007). Older employees compare themselves and are compared with the educational credentials of younger generation (Ruoholinna 2009), and acquisition of a degree at age 50+ can be seen as a way of gaining a more competitive position in working life (Isopahkala-Bouret, in review). Moreover, higher education studies in midlife may protect older employees from being subject to unfavourable age-related stereotyping and age-discrimination at work (cf. Irni 2010).

[1] This chapter draws upon a research project 'Ageing and expertise—Narrative inquiry into the experiences of older adults who acquire master's degrees in their fifties' (2011–2014). The project investigates why experienced professionals enroll in degree-oriented university programs in later life, and what kinds of benefits their new master's degree brings to their remaining professional career—and beyond. This research brings educational and sociological knowledge to the field of ageing research and contributes to the efforts of promoting active ageing and active employment of older people. The project is funded by Academy of Finland (Project number: 1253082) and it is associated with Future Leaders of Ageing Research in Europe (FLARE) program.

Prior studies have also shown that higher education studies in midlife may fulfil a long-term desire. Older people often want to study because they are curious and love learning or because they are genuinely interested in the subject of study (cf. Reay 2003). The importance of personal development and fulfilment as a trigger for higher education studies increases among those older students who approach retirement age (Jamieson 2007; Brennan et al. 2000). Universities can play a leading role in creating new types of active ageing and supporting older people as they plan what to do after their main professional careers (Phillipson and Ogg 2010; Phillipson 2010).

Retirement can be seen as a lengthy transitional process (Hodkinson, Ford, Hodkinson et al. 2008). Anticipation and preparation for retirement starts usually well before the actual beginning of a retirement pension. Some older employees have already in their fifties/early sixties made the decision to retire and they know the exact retirement date. Others still hesitate about how long they will stay actively involved at work. Such a pre-retirement phase can last years and involve progressive changes in health, social relations, and employment conditions (Hodkinson et al. 2008). Most importantly, learning is an integral part of it: 'As soon as a person starts to anticipate retirement, they are beginning to learn to see themselves, their situation, and the future differently' (Hodkinson et al. 2008, p. 179).

16.2 Research Questions and Methods

The starting point for this study is that universities offer adult learning possibilities and in that sense play a key role in promoting active ageing in society (cf. Phillipson and Ogg 2010; Phillipson 2010). University studies in midlife can influence the retirement anticipations and open up unforeseen prospects for active ageing. Specific research questions of this study are defined as follows:

1. What do graduates who have acquired a master's degree in their fifties expect from the forthcoming retirement?
2. What significance does university graduation in midlife have in regards to active ageing?

The study is based on 14 interviews with graduates who have acquired master's degrees in their fifties. Nine of them had acquired Master of Science (M.Sc.) degrees in Business and five had Master of Social Sciences (M.S.Sc) degrees from two research-oriented universities in Finland. Ten interviewees had first university degrees acquired in the 1970s or early 1980s, and four had acquired prior university degrees as adult graduates in the early twenty-first century. The age range of interviewees was 54–62 at the time of interviews, and they had graduated 1–5 years earlier. All interviewees were (or had been) in professional or managerial positions, in both public and private sector jobs. At the time of interviews, one was fully and one was part-time retired. Two of the interviewees were men and the remainder were women, which reflects a common gender division among older university graduates in Finland.

The interview schedule included questions relating to educational and professional life-history, motives for attaining master's studies in one's fifties, experienced outcomes of study, current work responsibilities, and future retirement prospects. Questions related to ageing and gender were also included. The idea was to understand how master's studies in midlife fitted into the long-term patterns of stability and change in the narratives of participants. Interviews lasted from approximately 60–90 min. They took place at the university or the interviewees' work place, and one interview was conducted via telephone. All interviews were tape-recorded and transcripts were written based on these tape-recordings. Interviews were originally conducted in Finnish and the citations used in this chapter were translated by the author. When significant ambiguities arose, other translators were consulted.

The analysis focused on interviewees' accounts in which they discussed their retirement prospects. During the interview, people were asked: 'Does your master's degree have a meaning for you that goes beyond the active years of employment?' and as a response people were speaking about their anticipated late career and retirement time. Such accounts can be called 'future narratives' in the sense that they preserve the characteristic feature of future time, namely that it is yet undecided, open, and multiple, and that it has not yet crystallized into actuality (Bode and Dietrich 2013). Such narratives provide a view of uncertain, but possible future scenarios (Uprichard 2011). These future accounts were analyzed in the context of the overall professional life histories, and especially the various reasons why these interviewees wanted to conduct master's studies in their fifties and the kinds of outcomes they had experienced. Narratives of the future are dependent of the narratives of past and present (Uprichard 2011). I used a variety of analytical foci to interpret narratives (Riessman 2008): I acknowledged both the content and the storyline, and I paid attention to rhetorical and discursive aspects of narration. I was also aware of the cultural meta-narratives of age and ageing (Gullette 2003) and how they shape the individual experience.

In a narrative study there are ethical considerations that need to be taken seriously. The interviewees gave their oral and written informed consent to participation. They were informed that they had the right to withdraw at any stage, and that the collected data would be treated with confidentiality. I used pseudonyms to protect participant anonymity. The following details were removed from the citations used in this chapter: places of residence, names of the work organization, job titles, specific job responsibilities, names of family members, colleagues, etc. I also changed some minor details in the narratives, which were considered to be insignificant, in order to protect anonymity.

16.3 Anticipating Active Ageing

A great majority of interviewees could see the continuum between their academic studies, professional knowledge and skills they had acquired, and the activities they anticipated to be involved in later life. In the following, I will elaborate in detail what these activities were and how university studies in midlife had significance for them.

16.3.1 Continuing Working as Long as Possible

University studies in midlife increased work motivation. Most of the older graduates thought that the master's degree acquired in their fifties gave them a 'new start', novel professional openings, and strengthened their feelings of continuing working. Especially those who still had a good 10 years before the official retirement age—which in Finland usually starts at the age of 63 and can be flexibly postponed until age 68—could not think of stopping working even at that age. They wanted to continue as long as they could in employment or alternatively in a self-employed mode. One woman had already started her own enterprise and planned to continue working although she was about to start receiving her pension in the following year. Two other women had a secondary occupation alongside with their main occupation, and they planned to continue working with those businesses while otherwise retired. To continue working in a part-time mode at the end of one's professional career was also seen as a favourable option among several interviewees:

> The first opportunity for me to retire would be in four years.
> And somehow I'd like to do it so that I wouldn't fully retire.
> As an alternative, I would like to retire gradually.
> I mean, for example, then at age of 63,
> I would start working part-time, like three days per week. (Tom, 59, operations development and marketing)

Many of the interviewees stated that work had been a very important part of their life. Some women emphasized that especially now in their fifties, when children have grown older and domestic duties diminished, work was one of the main sources of satisfaction: 'It would be terrible to not have a job, like you would just wait to be retired.' One could speculate that those interviewees, who already had had rewarding and interesting jobs prior to their university studies, would have in any case prolonged their working careers. Then, what was the added significance of the new degree at the age of 50+?

First of all, those who had transferred to a new job after graduation explicitly stated that graduation at the age of fifty carried a special significance. A new degree was a kind of a proof against ageist stereotypes, which assume that old people do not know information technology and have no proactivity and creativity anymore, for example. Those who did not change jobs, but got a permanent contract instead of a temporary contract (i.e. all of those who became qualified social workers) made also age-related justifications. They noticed that with the right kind of degree, they could have a good employment even if they were 50+. Furthermore, the new degree increased self-confidence and strengthened professional identity, and made older graduates feel more useful and able to contribute to their work. Last but not least, nobody could question their expertise now that they had up-to-date qualifications. (See in more detail: Isopahkala-Bouret, in review).

As a special case, one of the interviewees, Helen, had acquired a master's degree from a completely new domain and started a new professional career in midlife. She had first studied natural sciences in her youth and worked as a researcher. Some 20 years later, she moved to a domain of social services, accomplished a master's degree,

and became a qualified social worker at the age of 52. As she described her situation, she was still relatively new in the domain and eager to learn and to become a better professional: 'I have a feeling that I haven't still seen and experienced everything.' For her a forced early retirement would have been very frustrating. So, she was welcoming the Finnish pension reform that allowed people to work until the age of 68.

I'm going to be working,
I'll stay at work as long as they keep me and I'm allowed to be here.
(…I'll continue for) a long time still, at least until I'm 68 years old! (…)
I believe that this work can be done, in one way or the other, as long as you wish.
You can stay useful. (Helen, 55, social work)

It is common to prescribe a pre-retirement time as a process of gradual abandonment of demanding work duties (Hodkinson et al. 2008). The individual cases presented above showed the evidence that if older employees can upgrade their professional knowledge and skills, and are offered interesting challenges until the very end of their professional careers, they are both willing and able to continue working and postpone the start of their retirement. The social recognition and the feeling of 'being useful' were very important for older graduates who had plans to extend their professional careers.

16.3.2 'Cannot Even Think that I Would Not Use My Brain'

Two interviewees said immediately that a master's degree does not have any significance once you are retired. The professional competence, acquired during their studies, would not be applicable outside the working context. In that sense, their studies had no significance after retirement. The activities that they planned to be involved with once retired were not at all academic. They wanted to do sport, spend time in the summer cottage, garden, make art, take part in cultural events, and look after grandchildren, for example. Such activities were surely examples of active ageing, but did not require prior university education.

However, most of the interviewees stated that they could not imagine themselves being mentally inactive even if they stopped working. The interviewees asserted that intensive, goal-orientated studies in their fifties had impacted on their mental flexibility and on outlook on societal issues, among other things. They wanted to continue to use their brain and to do something intellectually demanding. Thus, university studies in midlife promoted active ageing in terms of both the ability and enthusiasm for continuous learning.

(Master's degree) has opened up my understanding on things, right?
And I know that: 'Ok. If I don't know something,
I can go to the library, I can go to the course, and I can get the knowledge!'
We have a lot of things that we don't know.
There are things that would be nice to know, nice to get to know better and to do.
It's not the end, for my opinion, when you reach the retirement age.
Like, you don't do anything anymore. (Helen, 55, social work)

For some of the interviewees this intellectual challenge meant formal education. Some universities offered possibilities for their alumnae to have an open access to

certain lectures, and Paula (61 years old, financial administration) was planning to take advantage of that after retirement. Many interviewees had already taken courses at the Finnish Open University, and in that institution access was not restricted by any kinds of age-limits. As everybody had enjoyed their own master's studies and found them beneficial, they were ready to also recommend that option as an alternative to the 'idleness' while (waiting to be) retired:

> Yes, of course, at this age you start thinking that
> if you still want to keep yourself in a good condition,
> you must use your brain and feet, or exercise.
> We've been thinking about this a lot.
> One old friend of mine became recently unemployed.
> And he has the possibility that he could just do nothing, you know,
> and wait to be soon retired after four years or five years, after four years.
> So, I've recommended him to go (studying). (Tom, 59, operations development and marketing)

A couple of interviewees shared their desire to do further studies and academic research. Two women had already topics of interest in mind, but they had not applied for the doctoral program. One woman had already completed all the courses required for a PhD. In the following, these intentions were narrated by using another person as an example of how to spend time in an active old age as an academic person:

> My husband has the same way of thinking as I do.
> He is already 65 years old.
> And he is, in a way, fully retired.
> But now he works full-time (for his PhD) at the university, which is different.
> He has the (similar business) background as I do.
> And now he has found this scientific world.
> He's actively working, you know.
> Or shall I even say that he's actively using his brain.
> Whether you do research, teaching, or consultation, or whatever it is that you do.
> But I can't even think of that I wouldn't use my brain (at old age). (Pia, 62, management consultancy)

Attainment in education can be seen also as a battle against ageing (Wilinska 2012). Lifelong learning can help to resist the biomedical and cultural decline narrative that associates old age with illness, mental decline, and death (Gullette 2003). As older graduates express positive attitudes toward education and learning, they position themselves as 'not-yet-old'. Curiosity and openness to changes and self-development are important for active ageing. However, there is a risk that continuous learning discourse takes middle-age as a norm and ignores old age (Wilinska 2012).

16.3.3 'I Will Contribute to the Society in New Ways'

Master's studies at the university had opened doors to becoming an active member in the alumni associations. At the time of the interviews, nobody had really had time to be actively involved as they already had many teams and networks at work in which they took part. However, this kind of networking with other alumni was seen

as potentially important after retirement when work contacts would diminish. Also other kinds of associations interested these older graduates as communities of which they could be part after finishing full-time, paid-work.

> I believe that (this degree) gives you possibilities in many different ways (after retirement).
> Like, for example, (it opens doors) for different kinds of (social activities).
> It enables you to be a member of the Economists' Association
> and to do all kinds of things, to be active there.
> So, it can bring you new hobbies and friends, real friendships.
> Like I don't have time now (laughs). I just don't have enough time for it. (Elisa, 55, service marketing and sales)

Moreover, volunteering through different kinds of associations, voluntary organizations, and schools was seen as a way to keep using the professional competence that had been acquired via long work experience and higher education. In this way, the master's degree that the interviewees had acquired in their fifties would also benefit the wider society. Finns in general are actively participating in voluntary work, and overall 40 % of those aged 65–79 years stated that they are active in voluntary work (Ehlers et al. 2011).

> I can imagine (that this degree will be useful after retirement).
> I'm thinking about many of my colleagues, who have retired.
> And very few of them have rested on their laurels.
> Most of them are doing some sort of voluntary work.
> And (in retirement) they've been able to use their professional experience.
> Quite a few of them have provided some training to immigrants, for instance. (Anita, 54, human resources management)

> I'm very interested in the environmental protection.
> And that's what I've been thinking (to do after retirement).
> I could do like some voluntary work on that domain.
> I could maybe (use my academic skills and) help in the communication duties.
> There surely could be such associations. (…)
> And then it would be very beneficial that I've accomplished this kind of very diverse degree. (Anna, 54, communication and marketing)

The type of volunteering that these interviewees were discussing was related to their academic studies in a way that they continued acting 'professionally'. In general, level of education is strongly influencing volunteering, but in prior studies older volunteers have not usually had a master's level education (Ehlers et al. 2011). Therefore, contrary to prior studies, the interviewees in this study were foreseeing themselves most of all in responsible volunteering roles, such as taking care of an association's communication, providing training, and running counselling groups. This kind of voluntary work differed from the common examples found in studies and policy reports discussing volunteering and active ageing. It is commonly assumed that older people volunteer in care-related and supportive tasks, such as assisting children, caring for disabled people, or providing home visits to isolated people with limited mobility (Ehlers et al. 2011).

16.3.4 Becoming Social Activists at Old Age

Prior studies have shown that older people become more sensitized to social problems through voluntary work, improved their knowledge about their own social rights and learn how to claim them, for example from the local authorities or the healthcare system (Ehlers et al. 2011). The interviewees of this study, especially those who had social worker qualifications, addressed directly how they already knew how the social system works, and therefore they could easily apply for all those social benefits for which they (or their relatives) were eligible. Their 'bureaucratic skills' helped them to deal with different public officials and to fill the needed forms and write the needed documents.

An academic degree had also provided skills that would enhance the agency of the interviewees at old age. The professional status that the master's degree had guaranteed could be turned into social activism at old age. In relation to that, three women told about their dream of writing. The ability to write was seen as a powerful means of influencing. One woman gave an example of how well-written language helps in conflicts and argumentation, and two other women were explicit about their intentions to use their writing skill for expressing public opinions on societal issues.

> In general, I've always liked to, I'm writing a lot. (…)
> I'm not currently active in social media,
> but in the future that could be one of those medium where I could write
> otherwise (I could publish) my opinions in the newspapers, you know,
> and to give public feedback. (Anna, 54, communication and marketing)

> I've always been very enthusiastic writer,
> and I've taken part in some small-scale writing competitions.
> So, I will need that writing compete a little bit everywhere (after retirement).
> For example, it provides credibility.
> If you, for example, want to complain about some public plans,
> you need to know the exact, formal language very well (laughs). (Anita, 54, human resources management)

Emma (56 years old) who had had a career as a social worker, stated that after retirement she could finally start campaigning against social problems she had faced during her professional and personal history. The financial independence provided by pension could liberate her from obedience to the employer. As long as she was still employed she could not fully criticize the working policies and the way things were handled at work and in her profession. But once retired, 'there's no longer a risk of being fired'. Moreover, the master's degree would give her the qualification and status that she needed for this kind of activism.

> (After retirement) you still have the status;
> you can always say that you've been working as a qualified social worker. (…)
> I always tease my (colleagues by saying) that
> when I'll have my last day (of work) before I retire,
> I'll not mince my words about that (one particular societal problem).
> Then, I'll yell that out!
> And I'll write about that to the (main Finnish newspaper).
> Then I dare to say my opinions fully. (Emma, 56, social worker)

These narratives about the anticipated future as a social activist can be taken as attempts to open up space for an alternative identity as an older women: 'Older women have greater opportunities for developing identities other than wife, mother, or paid worker, and for taking new roles and activities that they may have not had time for when younger' (Cassie 2011, p. 130). Older women may have more opportunities to act upon societal problems because they no longer have to follow the societal expectations placed on women in general. Moreover, here the activism is not (only) targeted to 'age-based' issues, such as pension and elderly care, as the dominant model of resistance in later life would assume (Grenier and Hanley 2007).

16.4 Discussion

The findings of this study showed that degree-oriented studies in midlife impact positively on active ageing. The majority of older graduates stated that their master's studies had helped them to stay active at the end of their professional career and even made them willing to prolong their career. Many of these older graduates wanted to continue in paid work—at least part-time—after the minimum age of retirement. Moreover, most of them expected to stay mentally active after retirement, and some had plans for further study.

On the other hand, some older graduates anticipated to take part in voluntary work after retirement. The type of voluntary work they predicted to be involved with required academic knowledge and skills. Also the social activism that some older graduates wanted to take part in was enabled by the qualifications and social status of master's level education. University studies in midlife broadened the options for active ageing.

In their future narratives, older graduates were 'extending the middle-age' as they were planning to prolong their career and work-related roles. However, they were also making space for 'agentic old age' in terms of volunteering and societal activism. In their future prospects they continued to have an important and meaningful place in the society. As most of the interviewees were women, this shows the potential of well-educated, older women in the society. Their anticipations were strongly promoting active ageing.

However, we do not know what will actually happen once these people are retired. Critical theorists have argued that the social categories of 'retired' and 'old' are depowering and provide restricted opportunities for agency. At retirement people have less societal and cultural power; to be regarded as 'retired' does not provide similar credibility as when one acts in a position of an employed professional (Ojala 2010). Furthermore, social activism requires particular determination as older women are generally not expected to cause problems, make demands, or engage in direct resistance and action (Grenier and Hanley 2007).

Degree-orientated studies in midlife are significant for 'agentic' active ageing especially because graduation can provide a recognized social status. Having a master's degree is a credit that will not disappear after the professional career and work-related, professional roles disappear. Older people with academic status, and

upgraded knowledge and skills, are better equipped to look after their own social rights and to continue being active citizens in society. Highly educated people have also better social position and more resources to fight against ageist stereotypes (Irni 2010; Cassie 2011).

Those who accomplish university studies in midlife are not a homogeneous group. This study has focused on those older graduates who had prior professional education and experience, and who were actively involved in working life after graduation. Their experiences do not reflect the experiences of those older graduates who have other kinds of backgrounds. There are also older students who are attaining university level qualifications for the first time, have prior work experience from nonacademic jobs, and/or who have been unemployed prior to their studies. Moreover, there are older students who are voluntarily out of the labour market. In any case, university studies have a high potential to contribute to active ageing.

To conclude, those people who graduate in midlife with master's degrees have the capacity to become part of the societal change that truly promotes active ageing. As they are getting older and eventually retire, they keep learning, working (voluntarily), and actively promoting societal well-being. This study has provided new interpretations on the relation between higher education in midlife, late career, and retirement prospects. Particularly it has shown what impact an academic degree can have for increasing opportunities to exercise agency at old age. The results of this study will benefit the future of multidisciplinary and interdisciplinary ageing research by bringing in a new research topic and by strengthening the focus on the educational gerontology and ageing at work. This study will also benefit the policies of lifelong learning and active ageing by emphasizing how important the higher education opportunities in midlife are for the later life prospects.

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Chapter 17
Perspectives on Dynamic Retirement and Active Ageing

Monika E. von Bonsdorff and Mikaela B. von Bonsdorff

17.1 Introduction

The workforce in many developed countries, particularly in Western Europe and Japan, ages due to low fertility and high life expectancy rates (Walker and Maltby 2012). This trend raises concerns regarding labour force participation rates and subsequent changes in potential economic growth (Hardy 2006; Hedge et al. 2006; Ilmarinen 2006; United Nations 2011). Global ageing will have a remarkable social, political, cultural, and psychological impact on individuals, as well as on national, international, and small-sized communities (Ilmarinen 2006). It will also have an effect on working life in terms of the possible lack of new workers entering the labour market, the labour shortages, and the short-term funding of pensions. Additional work life issues concern quality of working life, age discrimination, promoting health in the workplaces, and restructuring work (Wang and Shultz 2010).

Work is an essential part of most individuals' lives from early adulthood to old age. It is natural that individuals' ageing is present in the workplace and that ageing affects individuals as well as collective work performance in many ways. Individuals' ageing affects various domains and encounters an array of physical, mental, and societal changes during the process (Baltes and Baltes 1990). It is not surprising that the ageing of the workforce is reflected in the need for deeper theoretical perspectives together with practice-oriented innovations in the field of organizational research.

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Psychologists may well have a key role in understanding the socio-behavioural change in the interrelationships between population ageing, economic growth, and the acceptance and adaptability of older employees in the workforce (Phillips and Siu 2012).

Sufficient physical and mental health and resources are a prerequisite for employees' ability to continue working in old age. Work ability indicates the balance between employees' personal resources and work demands (Ilmarinen 2006, 2009). As work ability tends to decline with age (Ilmarinen and Tuomi 2004), a concept was developed as a response to challenges brought on by early exit from working life. Declining work ability predisposes people to work disability, spells of sickness absence, early retirement from employment (Ahlstrom et al. 2010; Alavinia et al. 2009; Sell et al. 2009), and even disability in old age (von Bonsdorff et al. 2010). By emphasizing the dynamic balance between the work demands relative to the employee's physical, psychological, and social resources, the concept of work ability is useful when promoting better working lives and active ageing (Ilmarinen 2009). Active ageing is described by the WHO (2002) as "… the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age".

On the individual level, ageing is typically tied to changing physical and mental capacities and planning one's career in later life. The central goal is to transition successfully into retirement and to lead a satisfying life in retirement (Wang and Shultz 2010). While retirement indicates withdrawal from work, a more dynamic perspective on retirement can also include involvement in working life. Bridge employment, which often is described as the transition into some part-time, self-employment, or temporary work after full-time employment ends and permanent retirement begins (Feldman 1994; Shultz 2003), is a common way in the USA to gradually decrease work commitments in old age. Continuing in paid work or in self-employment in retirement is still not typical in Nordic countries. Nevertheless, recent changes in Finnish pension legislation in 2005 promote bridge employment.

The findings regarding the effect of retirement on health are conflicting. Some studies report that health, especially mental health, improves shortly after retirement (Drentea 2002; Mein et al. 2003); some that it deteriorates, e.g. in terms of work ability (Alavinia and Burdorf 2008; Buxton et al. 2005); and some that it has no effect (Ekerdt et al. 1983; van Solinge 2007). Some of these studies include disabled retirees, others non-disabled retirees. A recent study showed that retirement had a positive effect on all employees' perceived health—especially those who had retired from poor working conditions (Westerlund et al. 2010). When considering retirement and health-related outcomes, it is important to take endogeneity into account, as poor health is a typical cause for early retirement (Kelly and Dave 2011).

This chapter will present some of the current topics in the ageing research from a work life perspective. First, we discuss the *role of individual resource allocation strategies and human resource management in promoting the work ability of older employees*. Next, we discuss *personality and bridge employment in the Finnish context* as a means of extending work careers and applying a dynamic late-career perspective. Finally, we discuss the *effects of normal,* i.e. *after reaching full retirement age, and disability retirement on employees' objective health* measured with use of hospital care centred around retirement.

17.2 Dynamic Retirement and Active Ageing

The ageing process affects individuals in numerous ways in the working life context. Next, we will highlight some of these themes.

17.2.1 Prolonging Work Careers: Individual Adaptation, Human Resource Management Practices, and Work Ability

As the workforce in industrialized countries ages, promoting health and well-being, as well as maintaining the work ability of ageing employees, becomes even more pressing, both for individuals and organizations. Work ability has its origins in occupational health literature, but has since evolved from a medical idea towards a more holistic and versatile construct where work ability is created and promoted by many factors (Ilmarinen 2006; Ilmarinen et al. 2008). This concept is also related to successful ageing, which in turn is likely to involve adaptation, control, productivity, social competence and skills, self-mastery, cognitive efficiency, and social functioning (Baltes and Baltes 1990).

It is commonly recognized that job characteristics are salient predictors of employee's health and well-being (see Kulmala and von Bonsdorff 2014). A body of evidence suggests that work can have detrimental effects on individuals' health and result in lower ability to work, especially when the employee's resources and job demands are not in balance (Bosma et al. 1997; Kivimäki et al. 2002; Tuomi et al. 1997). Ground-breaking findings show that high work-related mental strain (Johnson et al. 1989; Marmot et al. 1997; Niedhammer et al. 2011; von Bonsdorff et al. 2012) and physical strain (Amick et al. 2002; Bourgkard et al. 2008) predict poor health and even mortality. Furthermore, high demand jobs together with low control and social support are significant predictors of coronary heart disease (Belkic et al. 2004; Kivimäki et al. 2008).

Prior research has shown that work ability, especially in the age group between 52 and 58 years, tends to decline dramatically (Ilmarinen and Tuomi 2004), even if these changes vary in both onset and speed (Gould et al. 2008; von Bonsdorff et al. 2011). Furthermore, extensive evidence shows that poor work ability predicts such work-related significant outcomes as work disability, spells of sickness absence, early retirement from employment (Ahlstrom et al. 2010; Alavinia et al. 2009; Sell et al. 2009), and even disability in old age (von Bonsdorff et al. 2010). Against the background of changing global age demographics, it is of utmost importance to promote work ability and help ageing employees to maintain their work ability.

By balancing the work demands relative to the employee's physical, psychological, and social resources, work ability can be promoted (Ilmarinen 2009). In addition to employees' health and other personal resources, work ability is built and determined in relation to the job and surrounding society. More specifically, work ability is created and sustained by many factors, such as better *age management,*

which refers to daily management practices that take employees' age and age-related factors into account (Ilmarinen 2006; Ilmarinen and Tuomi 2004). These actions may include providing ageing employees with training opportunities, competence development, and learning as means of preventing negative changes in perceived work ability (Solem 2008). On a broader scale, promoting work ability means taking work demands, the environment, work organization, and an employee's health, functional capacity, and competences into consideration (Tuomi et al. 2001).

The resource-based theory can be used to tie together the concepts of work ability and employees' strategies to allocate their resources, i.e. *selection, optimization with compensation* (SOC) (Baltes and Baltes 1990). According to Hobfoll's (2002) theory, individuals build, protect, and retain their resources. The theory further states that when faced with loss of resources, an individual will experience distress and may consequently develop mental and physical health problems (Hobfoll 1989; Hobfoll 2002). Physical health and mental well-being are central aspects of employees' ability to work in that the perception of one's work ability is dependent on physical, mental, and social resources. Resources are at the core of SOC as well. The SOC model, developed to provide a model for successful ageing, postulates that as individuals age, their physical, mental, and social resources tend to diminish (Baltes and Baltes 1990; Baltes 1993). In order to adapt to these changes, individuals can use selection, optimization, and compensation. The model has been frequently used in the work context. Studies have found that the use of SOC strategies can balance the effect of constrained resources on various work outcomes, such as productivity, focus on opportunities, and work ability (Abraham and Hansson 1995; Weigl et al. 2012; Yeung and Fung 2009; Zacher and Frese 2011).

More specifically, the SOC model describes a general process of adaptation to age-related changes in one's resources (Baltes and Baltes 1990; Baltes 1993). Individuals are likely to use SOC strategies in situations where they need to adapt to developmental losses and challenges throughout life (Baltes and Baltes 1990). In the work context, the use of SOC strategies can be effective, provided that job demands are sensitive to age-related losses and older individuals have the opportunity to use SOC strategies. The theory involves three interacting elements and processes: selection, optimization, and compensation. The first element, selection, refers to setting goals and deciding on their priorities by restricting one's activities to more important domains (Baltes and Baltes 1990). In the work context, individuals might choose to focus on tasks they find interesting and inspiring instead of goals they cannot accomplish anymore. The second element, optimization, refers to people engaging in behaviours to enrich and expand their general reserves in order to achieve in their selected goals. In the work context, this can mean rescheduling time and refocusing energy or learning new skills. The final element of SOC, compensation, results from the restrictions in individual resources and the successive use of alternative means to achieve goals. This restriction is experienced particularly at times when situations and goal characteristics require a wide range of activity and high-level performance. In a work context, compensation can involve developing existing skills, utilizing substitute skills, or rescaling goals.

Both work ability and SOC are highly intertwined and interact with the surrounding work organization. It is an integral element when designing a study on promoting work ability. Furthermore, it has been shown that autonomy at the work place promotes both work ability (van den Berg et al. 2009) and the use of SOC strategies (Abraham and Hansson 1995; Bajor and Baltes 2003; Baltes and Dickson 2001). These findings can be understood in the light of the *Conservation of Resources* theory (COR), which regards job autonomy as a contextual resource (Hobfoll 2011). Of direct relevance, a study showed that job autonomy moderated the relationship between SOC and work ability so that under high job autonomy, the use of SOC strategies was associated with better work ability (Weigl et al. 2012). It would thus indicate that high external resources can compensate for low personal resources in the work environment.

A broader perspective on contextual resources besides job autonomy can be found in human resource management practices called *high involvement work practices* (HIWP). They typically cover a broad set of management practices, including performance-based rewarding, employee participatory programs, teamwork, information sharing, training opportunities, promotion programs, etc. (Gutherie 2001). Even if these practices have not been studied in the context of work ability yet, a positive connection has been found between HIWPs and enhanced organizational productivity (Huselid 1995; Gutherie et al. 2009; Martín-Tapia et al. 2009; Sun et al. 2007), employee retention (Gutherie 2001; Huselid 1995), job satisfaction and affective commitment (Mendelson et al. 2011; Ramsay et al. 2000), and well-being at work (Harmon et al. 2003; Vanhala et al. 2009).

Some preliminary findings indicate that the use of SOC strategies at work is either directly related to perceived work ability (Müller et al. 2012) or indirectly associated with supervisor evaluated work ability (Weigl et al. 2012). Nevertheless, there is to date relatively little evidence on how individuals can effectively channel their dwindling resources in order to counterbalance the age-related resource losses. Furthermore, there is a need to better understand the role of individual resource allocation strategies as well as formal human resource management practices in helping older employees maintain their work ability.

17.2.2 Bridge Employment as a Late-Career Developmental Stage

Changing age structures and the number of older employees in the workforce has probably contributed to the interest in late-career transitions. Bridge employment has been defined as a pattern of labour force participation of older workers as they disengage themselves from their previous career jobs and gravitate towards a permanent exit out of working life (Shultz 2003; Wang and Shultz 2010). Bridge employment can involve continuing to work after retirement in a career job or taking up a job in a different field (Feldman 1994; Shultz 2003). A dynamic view of

bridge employment, which examines bridge employment as a longitudinal workforce participation and retirement transition process (Wang and Shultz 2010), may help us capture the adaptive element in the bridge employment process. Furthermore, bridge employment decisions are used as a means in the retirement transition process by the employees themselves, often driven by the motivation to adjust to life in retirement (Wang 2007; Wang et al. 2008). More specifically, individuals who have been deeply involved in their work may try to sustain their daily routines by participating in activities they value highly (Gobeski and Beehr 2009). According to the continuity theory, which is widely used in understanding bridge employment (Wang and Shultz 2010), the work environment offers a natural way to maintain continuity through daily routines and engaging in social interaction with colleagues, supervisors, and clients (Atchley 1989).

According to Wang and Shultz (2010), bridge employment can be conceptualized as an informed decision-making process, where employees who were satisfied with their financial situations, had flexible jobs, and felt that they could retire through their own choice wanted to continue in bridge jobs (Weckerle and Shultz 1999). Bridge employment can also be viewed as a career development stage (Wang and Shultz 2010). Some of the most significant predictors of engaging in career bridge employment, which means continuing to work in the same job or in a similar job, are younger age, higher education, good health, low job stress, and job satisfaction (Davis 2003; Kim and Feldman 2000; Wang et al. 2008; von Bonsdorff et al. 2009). In addition to these factors, employees with better financial conditions thought about bridge employment in another field over early retirement (Wang and Shultz 2010).

Recently, studies on factors associated with bridge employment have focused on work-related psychological factors. Besides health, these factors seem to be significant in bridge employment decision-making. According to Kim and Feldman (2000), the older the employee becomes, the more unlikely he/she is to achieve continuity in life through work, due to health limitations. As working conditions may have a long-term effect on employees' health, work can be a positive force for middle-aged and older employees in terms of job satisfaction, the possibility to develop oneself, and job control, which results in participation in bridge employment (von Bonsdorff 2009).

While health-related factors may influence bridge employment decisions, little is known about the effects of personality (Feldman and Beehr 2011). The consensus is that personality can be captured by five traits called the Big Five (McCrae and Costa 1987): Openness to experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. In a theoretical sense, personality may influence certain biographical events, such as retirement, in terms of individuals' motivational priorities, coping strategies, and emotional responses (McCrae and Costa 1987). Studying personality traits in relation to retirement is further warranted, as prominent theories on ageing differ in how they link personality and retirement together (Löckenhoff et al. 2009). More specifically, disengagement theory (Cumming and Henry 1961) suggests that changes in personality precede retirement, as retirement indicates withdrawal from working life as a result of older employees' declining resources. In contrast, activity theory (Havighurst 1961) and social investment perspective (Kim and Moen 2001)

emphasize role loss, which in turn would indicate that personality can change after retirement. Finally, continuity theory (Atchley 1989) suggests that individuals' personality remains unchanged throughout the retirement process.

Empirical evidence indicates that A-type behaviour characterized by hard-driving, aggressive, impatient activity might be one of the individual variables related to retirement intentions and that these persons would prefer to continue working instead of retiring (Beehr 1986). Certain types of personality traits from the Big Five (McCrae and Costa 1987), namely, Extraversion, Conscientiousness, and Agreeableness, have been found to predict work-related variables, such as high job satisfaction, high job performance, and even good interpersonal skills at work (Judge et al. 2002). There is also some indication that Openness to experiences is associated with older adults' life satisfaction (Stephan 2009) and low Neuroticism around age 60 predicted higher satisfaction with retirement (Vaillant et al. 2006).

More recently, Blekesaune and Skirbekk (2012) found that Neuroticism increased the risk of disability retirement among women, whereas Openness increased the risk for men. Parallel to these findings, Löckenhoff et al. (2009) reported in a community-based longitudinal sample that personality did not predict future retirement and that personality remained unchanged during the retirement process. Another longitudinal study also found that retirement did not alter the course of trajectories on Neuroticism and Extraversion (Mroczek and Spiro 2003). These findings are consistent with continuity theory, which states that the identity and self-concept of the individual retiring does not differ before, during, or after retirement (Atchley 1989).

Studying personality in terms of bridge employment calls for longitudinal data, preferably spanning from midlife to old age. This allows researchers to identify development trajectories in personality characteristics and professional identities and combine these findings with midlife outcomes, which can help us interpret the effect of individual determinants on bridge employment intentions. As Wang and Shultz (2010) point out, personality variables have shown a good prediction value on transition and adjustment quality in other types of life transition and adjustment. Hence, personality variables may have an important impact on individuals' coping style and social behaviours. Finally, it may be that the association between personality and bridge employment is mediated by several variables, such as job satisfaction and pay satisfaction.

17.2.3 Retirement and Health Outcomes

Despite improved health and longevity in the last decades, the growing rate of early retirement due to disability burdens the economy of many OECD countries (OECD 2010). In addition to grappling with increasing disability rolls, ageing of the population is reflected in growing healthcare expenditures (OECD 2012). All Finnish citizens over 16 years of age who live permanently in Finland are insured by the residence-based national pension system, which provides a minimum income for retired individuals. In case of disability, the individual is entitled to certain benefits,

such as rehabilitation benefits and disability pensions. Besides unemployment pension, disability pension has been one of the main early exit ways from work life since the Second World War. While the unemployment pension was abolished in the 2005 pension reform, in 2011 65 % of Finnish pensioners retired due to reaching full retirement age and 32 % due to disability at an average age of 59.7 (Finnish Centre for Pensions 2013).

While the association between poor health and early retirement is well known (Wang and Shultz 2010), the connection between retirement and health remains somewhat unclear. Nevertheless, retirement as major life event is likely to affect health, lifestyle, and general well-being (Elder 1995). Empirical evidence on the effect of retirement on subjective and objective health remains inconsistent. Given the wide variety of health-related outcome measures and several other factors, it is difficult to determine whether transitioning into retirement has positive or negative or no effects at all on health in later life. Previous research has led to mixed findings: some studies have found positive effects of retirement on self-rated health and other health outcomes such as mental health, use of antidepressant medicine, and mortality (Jokela et al. 2010; Laaksonen et al. 2012; Mein et al. 2003; Mojon-Azzi et al. 2007; Oksanen et al. 2011; Westerlund et al. 2009; Westerlund et al. 2010); some studies report negative effects (Alavinia and Burdorf 2008; Bossé et al. 1987; Buxton et al. 2005) or no effects at all (Butterworth et al. 2006; Ekerdt et al. 1983; van Solinge 2007; Villamil et al. 2006). For a review on the associations between retirement and cognitive function, see Leist and Mackenbach (2014).

Most of the recent studies on retirement and health, which have typically followed retirees for 3–4 years after retirement, have concentrated on the effects of disability retirement on use of psychotropic medication (Laaksonen et al. 2012; Leinonen et al. 2013; Oksanen et al. 2011; Reitzes et al. 1996). Focusing on mental health problems is understandable, since it is a common diagnosis which entitles people to disability pension in Finland. These studies witnessed a significant increase in the use of psychotropic medication, mainly antidepressants, followed by a postretirement decrease especially among the disability pensioners (Laaksonen et al. 2012; Leinonen et al. 2013; Oksanen et al. 2011). The results suggest that disability retirement due to mental health problems may have a positive health effect.

Trajectories of self-reported health are another common outcome in the field of retirement and health. Retirement has recently been linked to increases in perceived health (Westerlund et al. 2009) and decreases in mental and physical fatigue (Westerlund et al. 2010). These studies used materials from the French GAZEL study with a 7-year postretirement follow-up. Interestingly, it was also found that poor perceived health did not affect those with optimal working conditions (Westerlund et al. 2009). Further, retirement did not change the risk of major chronic diseases (Westerlund et al. 2010).

Mortality as a health outcome has been used in several retirement studies. More specifically, a connection between disability retirement and mortality, which was only partly explained by underlying diseases, has been established (Gjesdal et al. 2009; Karlsson et al. 2007; Wallman et al. 2006). Karlsson et al. (2007) found in their prospective population-based study with a 12-year follow-up on individuals

aged 16–64 at baseline that mortality was especially high among the youngest disability pension recipients. Parallel findings were reported by Wallman et al. (2006), in a study which included data from five longitudinal cohorts. A different finding was reported by Gjesdal et al. (2008) who found higher mortality among female disability pensioners with a severe medical condition and among men with low socioeconomic status.

To date, the cause of high mortality among disability pensioners remains unknown. The association between these factors is somewhat surprising, as disability pension is typically granted on grounds of nonfatal diseases (Wallman et al. 2006). A possible explanation might be found in socioeconomic factors, which have to be taken into account when considering factors underlying disability retirement and mortality (Gjesdal et al. 2009). Of direct relevance, studies show that low socioeconomic status predicts poor health, long-term sickness absences, and subsequent disability pension (Gjesdal et al. 2008). Despite these results, some studies did not find significant effects of psycho-socioeconomic factors and underlying diseases in the association between disability pension and mortality (Wallman et al. 2006). In order to find out what other factors are at work here, further research is definitely warranted.

Inconsistencies in the findings on retirement and health outcomes may stem from structural and/or statistical endogeneity (Calvo et al. 2013; Kelly and Dave 2011; Neuman 2008).

The two types of endogeneity and ways to address them are outlined in the following. To control for *structural endogeneity*, which refers to a potential reversed causality in the relationship between timing of retirement and health, researchers suggest using longitudinal data sets and taking the timing of retirement into account (Calvo et al. 2013; Kelly and Dave 2011). This approach would also mean controlling for preretirement health beyond the baseline measurement. Performing longitudinal within-participant analysis, trajectories, on the health variables covering the retirement window may help account for endogeneity. Another attempt to control for structural endogeneity is to take into account the reason for retirement (Jokela et al. 2010). More specifically, this might mean grouping pensioners according to type of pension and even according to type of disease in case of disability pension (Jokela et al. 2010; Laaksonen et al. 2012; Leinonen et al. 2013; Oksanen et al. 2011).

Statistical endogeneity implies that unobservable factors may influence both the decision to retire and his/her health trajectory (Kelly and Dave 2011). These confounding factors are numerous and they can be divided into time-invariant or time-variant ones. Health and spousal occupational activity behaviour are some of the important time-variant factors, which ideally should be measured at multiple time points during the transitioning into retirement.

A further fact that may produce inconsistencies in the retirement and health outcome studies is related to study materials. Studies tend to adapt different time perspectives, with follow-ups varying from 1 year up to several decades. Some have even used cross-sectional materials, which makes it impossible to account for causality. Most of the recent studies focus on a 6–10-year time period before and after retirement (Laaksonen et al. 2012; Leinonen et al. 2013; Oksanen et al. 2011; Westerlund et al. 2009, 2010), which makes them comparable to some extent.

17.3 Discussion

In this chapter, we have introduced some of the current themes in ageing and late-career research. These themes, which span midlife to old age, adopt a positive perspective, focusing on individuals' resources, and dynamic participation in working life and health in old age. On the one hand, individual level findings presented in this chapter will in many ways be reflected on the societal level, e.g. in the form of older employees' participation in working life, even working in retirement. On the other hand, when adopting an organizational perspective, we can notice that effects of retirement policies and organizational management practices, such as *age management* or *HIWP*, cascade down to the individual employees. More specifically, human resource management practices can in many ways help older employees maintain their work ability. Furthermore, it would appear that disability retirement is beneficial for employees' perceived health, particularly mental health in later life. Thus, enabling exit from working life due to disability retirement seems warranted in the light of later life health. Other links between dynamic retirement and active ageing are less established. In the following, we discuss open research questions, followed by several indications for further research.

17.3.1 Use of SOC Behaviours, High Involvement Work Practices, and Work Ability

Previous research has established that work ability can be viewed as an indicator of successful ageing (Weigl et al. 2012). While health-, lifestyle-, and work-related factors are the strongest predictors of work ability (Alavinia et al. 2009; Ilmarinen et al. 1997; van den Berg et al. 2009), little is known of the role of individual resource allocation strategies, for example, use of SOC strategies, and human resource management practices, such as HIWPs in this equation. Still, previous research indicates that both use of SOC behaviours (Müller et al. 2012) and management practices (Ilmarinen and Tuomi 2004) are important in terms of maintaining and promoting older employees' work ability.

While it may be that work ability tends to decline at an individual speed in old age (Ilmarinen and Tuomi 2004), the role of age in the association between use of SOC strategies and work ability and other work outcomes is more difficult to interpret. First, previous results regarding age and the absolute level of SOC strategies have been somewhat mixed. Even the SOC theory proposes that older individuals can either use more SOC strategies to compensate the age-related reduction in resources or that they may not have sufficient resources to execute SOC behaviours in advanced old age (Freund and Baltes 1998).

Second, the research findings may be shaped by the fact that the use of SOC strategies and different outcomes has mainly been studied in selected age groups with age-dependent outcomes. More specifically, work-family conflict typically concerns young and middle-aged individuals with child-rearing responsibilities, while job performance and work ability concern all employees. The relationship

between use of SOC strategies and successful life management or well-being (Wiese et al. 2000, 2002) has been studied in a 3-year follow-up among individuals initially aged 25–36. Other studies have focused on the old and very old individuals aged 73–103 years (Freund and Baltes 1998). The use of SOC strategies and different types of job performance was studied among middle-aged and older employees (Abraham and Hansson 1995; Bajor and Baltes 2003; Wiese et al. 2002; Yeung and Fung 2009). When studying health-related outcomes and use of SOC strategies in older age groups, it is important to consider the selection aspect. Transitioning into full retirement at age of 63–65, or to disability retirement at a younger age, typically excludes individuals with health constraints who have retired before the beginning of data collection from these studies.

Third, studies reporting on the use of SOC, age, and work-related outcomes typically include mediator and/or moderator variables, which might make it difficult to disentangle the effect of age from, e.g. task difficulty (Yeung and Fung 2009), job complexity (Zacher and Frese 2011), or job control (Müller et al. 2012; Weigl et al. 2012). Findings in general indicate that age acts as a moderator in the relationship between use of SOC and various outcomes in that older employees benefit from using these strategies in terms of job performance (Yeung and Fung 2009), goal attainment (Abraham and Hansson 1995), and even work ability (Weigl et al. 2012). These previous results demonstrate the complex nature of the use of SOC strategies, age, and functioning in working life, which require further studies aiming at elucidating the complex mechanisms behind SOC use and work ability.

17.3.2 Personality and Bridge Employment Intentions

Health- and work-related psychological factors are salient antecedents of late-career decision-making, including bridge employment intentions (Wang and Shultz 2010). Poor health combined with high age is negatively associated with participation in bridge employment (Davis 2003; Kim and Feldman 2000; Wang et al. 2008; von Bonsdorff et al. 2009). Nevertheless, working conditions may have long-term effects on employees' health, as work can be a positive force for middle-aged and older employees in terms of job satisfaction, the possibility to develop oneself, and job control, which results in participation in bridge employment (von Bonsdorff 2009). While the health- and work-related factors may influence bridge employment decision-making, little is known about the effects of personality (Feldman and Beehr 2011). The fact that personality variables have shown a good prediction value for transition and adjustment quality in other types of life transition and adjustment (Wang and Shultz 2010) would suggest that personality may be of relevance in late-career decision-making.

Although Löckenhoff et al. (2009) found in their recent study that personality did not predict future retirement, they encourage further explorations. Consistent with continuity theory, which states that the identity and self-concept of the individual retiring does not differ before, during, or after retirement (Atchley 1989), it might be that socially active individuals (possibly extroverts) could find continuity in engaging in bridge employment. In particular, bridge employment in another field is likely to call for a certain amount of openness to new experiences.

17.3.3 Pre- and Postretirement Trajectories of Health Outcomes

Retirement is a major life event, which is likely to affect health, lifestyle, and general well-being (Elder 1995). In the light of current research on health and retirement, it is difficult to determine whether transitioning into retirement has positive or negative or no effects at all on health in later life. Several factors which may contribute to the inconsistencies in these study findings have been identified. First of these are structural and/or statistical endogeneity, which refers to a potential reversed causality in the relationship between timing of retirement and health or to the existence of an unobserved variable effecting both health trajectories and retirement decisions (Calvo et al. 2013; Kelly and Dave 2011; Neuman 2008). In other words, individuals in worse health tend to retire, or retirement is caused by ill health when in fact some other unobserved factor may influence both the retirement decision and health status at the same time (Neuman 2008). A further fact complicating the interpretation of findings on health and retirement is related to different time perspectives, with follow-ups varying from 1 year up to several decades.

While exploring the association between retirement and health outcomes, there are several issues that need to be considered. First, researchers should optimally use longitudinal data sets with multiple pre- and postretirement measurements of the health variables in question. Data should be population based and include both genders, as well as different employment groups including both blue- and white-collar workers. Furthermore, it is important to be able to take into account the reason for retirement, as these different reasons may be connected to different health outcomes. Second, in order to account for endogeneity, researchers should have sufficient longitudinal material on the health outcome, as well as factors besides health which may simultaneously influence both the decision to retire and health. Finally, the research window is dependent on the health outcome. If we aim to study the effect of retirement on immediate outcomes related to adjustment to retirement, such as perceived health or use of prescription medication, we may need a 6–10-year follow-up. If we explore the effects of retirement on old age health outcomes, such as old age mortality or use of hospital care, we need to have longitudinal data spanning midlife to old age.

17.4 Suggestions for Further Research

Several implications for further studies have been identified while reviewing various findings on dynamic retirement and active ageing. First, most research on work ability has focused on examining the individual level relationships between work ability and its antecedents and outcomes, such as sickness absence, disability, and old age functioning (e.g. Ahlstrom et al. 2010; Alavinia et al. 2009; Sell et al. 2009; van den Berg et al. 2009; von Bonsdorff et al. 2010). It remains unclear whether work ability can influence company level outcomes, such as company productivity. In addition, it is not clear whether employee age or company practices may be

associated to the work ability of the workforce in the company as a whole. Given that the collective work capacity of the employees indicates an important asset of the company (LePine 2005; LePine et al. 1997), it would be important to study the company-level antecedents and outcomes of work ability.

Second, the connections between personality and retirement (Blekesaune and Skirbekk 2012; Löckenhoff et al. 2009) might be mediated by several work-related factors. As Judge et al. (1999) point out, personality affects both extrinsic (income and occupational status) and intrinsic career success (job satisfaction). We also know that work-related factors are associated with bridge employment intentions (Feldman and Beehr 2011; Wang and Shultz 2010). Hence, it would be possible that personality would affect bridge employment intentions via, e.g. intrinsic and extrinsic career success. Future studies could explore, e.g. income and job satisfaction as potential mediators.

Third, as several researchers point out, the findings on retirement and health are inconsistent (Calvo et al. 2013; Kelly and Dave 2011; Neuman 2008). Hence, the retirement and health research might benefit from an objective health measure that would be more general in its nature rather than specific measures such as use of antidepressants and, at the same time, concern younger and older individuals at the same rate, rather than the use of mortality as a highly age-dependent measure. One possibility would be the use of a more generalizable health measure, such as use of hospital care in days which can be calculated as the duration between day of admission and discharge, defined as an overnight stay or day surgery in a central, district, or university hospital or health centre. These advancements in research on retirement outcomes are highly desirable to draw generalizable conclusions on the effects of retirement on later-life health.

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Chapter 18
Social Capital, Mental Well-Being, and Loneliness in Older People

Fredrica Nyqvist and Mima Cattan

18.1 Introduction

As the number of older people increases worldwide, policy and research strategies aiming to maintain older people's health and well-being have received wide attention at national and international levels (FUTURAGE 2011; Walker and Maltby 2012). Policy initiatives, such as Europe 2020, the European Commission's growth strategy (European Commission 2010) that framed the European Innovation Partnership on Active and Healthy Ageing[1] are long-term strategic frameworks for developing sustainable action to support healthy ageing. The purpose of the European Year for Active Ageing and Solidarity between Generations (2012) was to raise awareness of the contribution that older people make to society. It sought to encourage policymakers and relevant stakeholders to take action with the aim of creating better opportunities for positive and active ageing.

Active ageing is commonly defined as the development and maintenance of optimal mental, social, and functional well-being and capacity in older people (WHO 2002). It encourages people to live healthy and active lives and includes aspects such as participation, engagement, health, and security of older people, which fits well into the theories of social capital. Indeed, social capital is increasingly highlighted in health promotion and health research, including its potential ability to promote healthy and active ageing (WHO 2004). An underlying assumption is that social capital is good for mental well-being and research has over the last decades provided evidence that social capital tends to have health benefits (Almedon 2005;

[1] For more information visit http://ec.europa.eu/active-healthy-ageing.

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De Silva et al. 2005; Islam et al. 2006; Kim et al. 2008). However, to some extent research has ignored the significance of social capital for older people and its meaning for mental well-being. In this chapter we consider mental well-being as a positive aspect of mental health as opposed to a negative aspect, such as depression and mental disorders.

Social capital or social resources may benefit individuals' quality of life and well-being in later life (Nyqvist et al. 2013b). With increasing age, it is likely that the role of social capital for active and healthy ageing may also increase in importance as people rely more on interpersonal relations and social networks. Social activities, participation and trust, i.e., social capital, may be more relevant as a means for well-being when retired, due to loss of occupational attachment and work-based social networks. Participating actively in society and building trustful networks may thus promote social inclusion and enable active ageing, which in turn may lead to increased well-being.

In this chapter we will primarily focus on social capital and its meaning for mental well-being in older people. We will present empirical data on social capital and mental well-being such as the absence of loneliness in older people in three European countries. The analysis reveals variations in the pattern of social capital and mental well-being according to welfare regimes, an issue that has not yet been systematically investigated in older people. However, given that there is no "gold standard" of how to define or assess social capital or mental well-being, we start with a theoretical discussion on the concepts of social capital and mental well-being.

18.2 Social Capital

In the literature there are significant theoretical and empirical discussions concerning social capital. According to Kawachi et al. (2008) social capital embraces two distinct approaches, the social network and social cohesion approach. Within the social network approach the amount of various resources within the network constitutes social capital, and resources can be used in finding new jobs, receiving support, and accessing valued resources. This individual social capital approach is emphasized in the work by, for example, Bourdieu (1986) who underlined the amount of various resources within the network as social capital. The social cohesion or collective approach, as presented by Putnam (2000), claims that a society with high levels of participation and trust in others enhances interaction between people and that this is beneficial for individuals living in the neighborhood, community, or society. Within this latter approach social capital is mainly seen as a non-exclusive or public resource, or in other words, individuals can gain the benefits of living in an area with a high level of participation and trust, without necessarily having to participate and be actively engaged themselves. Coordinated actions between individuals enable people to pursue shared objectives that advance the collective welfare of society. For example, areas with high levels of social capital might be more effective at uniting people and ensuring access to health-related services,

support, and amenities which are important for older people. Social capital can thus have benefits for the wider community (Putnam) as well as for obtaining individual ends (Bourdieu). Given its dual focus on individual and/or collective features, analyses of social capital improve our understanding not only of individual resources of well-being but also of the influence of contextual or environmental features.

The social capital concept can also be defined according to its different components (Islam et al. 2006). Putnam (2000) separated two major elements of social capital: structural (e.g., social contacts, social participation) and cognitive (e.g., trust). The structural part describes the basis for generating social capital such as networks, relationships, and institutions that link people and groups together, while the cognitive aspect such as values, trust, confidence, and norms emerge from interacting members and through relations with one another. More broadly, structural and cognitive components of social capital underline the importance of accounting for the quantity as well as quality elements of the concepts. The relationship between the structural and cognitive component is, however, not entirely clear and it has been suggested that participation does not foster trust, as Putnam suggested; rather it is the trustful people who are already engaged socially (Hooghe and Stolle 2003). In empirical research the distinction is of relevance, since it seems that these two aspects influence health and well-being differently. For mental health the quality elements of the concept seem to be explicitly health beneficial (De Silva et al. 2005).

Social capital can also be seen as bonding, bridging, and linking. Putnam (2000) for example, separated two types of horizontal social capital: bonding and bridging. *Bonding social capital* refers to intragroup ties and is exclusive and may be characterized by homogeneity. *Bridging social capital* is more fragile than bonding but also more inclusive of heterogeneous individuals, and is usually seen as a more productive form of social capital at least when it comes to democracy building. Besides bonding and bridging social capital, Woolcock (2001), identified a third form, *linking social capital*, defined as relations between people with unequal wealth, power, and status. Within public health research the distinction between structural and cognitive social capital is common, as well as the distinction between individual and collective social capital, whereas less research has acknowledged the benefits of bonding, bridging, and linking social capital (Almedon 2005; De Silva et al. 2005; Islam et al. 2006; Nyqvist et al. 2013b).

18.3 Mental Well-Being

It is widely agreed that the concept of mental well-being is a complex subjective state that is difficult to define. This can be seen in the interchangeable and frequently concurrent use of the expressions "mental health" and "mental well-being." It could be said that the constructs of mental health and mental well-being reflect different disciplinary approaches and the perspectives of national and international policy drivers. The World Health Organization's definition of mental health states that mental health is "*a state of well-being* [our highlight] in which every individual

realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community" (World Health Organization 2007). Early definitions of mental health focused on subjective well-being consisting of positive and negative affect (Jahoda 1958; Bradburn 1969 in Bishop and Martin 2011, p. 298). Ryff (1989) proposed six theory-guided dimensions of positive psychological functioning, later referred to as "psychological well-being," comprising: self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth. These were shown to be components of people's overall well-being which was related to, but not identical with measures of subjective well-being, i.e., affect balance and life satisfaction (Ryff and Keyes 1995; Keyes et al. 2002). It also seems clear that individual life events affect cognitive and affective well-being, both in terms of magnitude and direction. However, it has been hypothesized that similarities may arise as a result of the level of control involved (Keyes et al. 2010a; Luhmann et al. 2012).

Lehtinen (2008), in a report to the European Union, suggested that mental health is an individual resource which comprises two dimensions: positive mental health (also referred to as psychological well-being) and negative mental health (or mental ill-health). Positive mental health can be conceptualized as a value in itself (Lehtinen 2008) or as including a positive sense of well-being, individual resources, the ability to develop and sustain satisfying personal relationships, and the ability to cope with adversity (Jenkins et al. 2008). This in turn is said to enhance an individual's capacity to contribute to family, social networks, the local community, and society at large (Health Education Authority 1997; Jenkins et al. 2008). Positive mental health can be described as "flourishing," meaning a combination of feeling good about and functioning well in life (Keyes et al. 2010a, b).

In the Foresight Mental Capital and Wellbeing Project, Kirkwood et al. (2008) define mental well-being as "a dynamic state that refers to individuals' ability to develop their potential, work productively and creatively, build strong and positive relationships with others and contribute to their community" (p. 19). Positive mental health is therefore more than the absence of illness or symptoms of mental disorders. Recently, some policy documents have used the expression "mental health and well-being" to denote a dynamic positive state of mind and body, feeling safe and being able to cope with normal stresses in life, and connect with people, communities, and the wider environment (see for example: Department of Health 2009; World Health Organization 2011). None of these definitions are age specific. However, the National Institute for Health and Clinical Excellence (NICE 2008) guidance on the promotion of the mental well-being of older people, which has been adopted by NHS Health Scotland (2010), defines mental well-being as a dimension of mental health which includes life satisfaction, optimism, self-esteem, mastery and feeling in control, having a purpose in life, and a sense of belonging and support.

The range of conceptualizations of mental well-being shows that despite some overlap between them, each of them includes additional and specific dimensions. This dissimilarity is reflected in the debate around the measurement of mental well-being.

Some authors have developed specific tools for the measurement of mental well-being (e.g., Stewart-Brown et al. 2009; Lamers et al. 2011), others have suggested the use of specific scales from existing validated measures (e.g., SF-36, WHO-5, GHQ-12, OPQOK; Bech et al. 2003; Hu et al. 2007; Lavikainen et al. 2006; Bowling 2009). Loneliness, or the absence of loneliness, is frequently used in association with measures of mental health in older people to denote quality of life or mental well-being (O'Luanaigh and Lawlor 2008). This will be addressed next.

18.4 Loneliness

Loneliness is often considered to be a problem of growing older. Although loneliness can be experienced at any age, older people are at greater risk of enduring loneliness because of a reduction in personal and external resources available to them (Dykstra 2009). It has been shown that about 50 % of the oldest old report serious or moderate loneliness, and that between 30 and 40 % of older people in the UK and other European countries are sometimes or often lonely (Victor et al. 2009), and this figure has remained fairly constant for the past 40 years. With the increase in the numbers of people aged 60+, the actual numbers of older people experiencing loneliness are also increasing.

Loneliness has been described as a mismatch between one's desired level of companionship and the relationships one has (Scharf and De Jong Gierveld 2008). Older people are at higher risk of health problems, such as mobility problems and sensory impairment, as well as decreasing social networks through the loss of spouse, close family members and friends, which puts them at risk of loneliness. In addition, residential relocation is common, moving from a family home to an institution, suggesting a change in informal relations. All these factors are associated with an increased risk of becoming lonely. Loneliness is associated with a wide range of physical and mental health problems and with a reduction in quality of life (Bowling and Gabriel 2007). Known risk factors include loss and bereavement, widowhood, perceived and actual poor health, lack of resources, living alone, and time spent alone (Scharf and De Jong Gierveld 2008).

Loneliness can occur as a result of one event, such as the loss of one's partner, or it can be chronic and made worse by the transition into old age. Research has shown that loneliness contributes more strongly to the variance in both physical and mental health than, for example, perceived social support (Stephens et al. 2011). There is now strong evidence that loneliness is directly associated with depression (O'Luanaigh and Lawlor 2008), reduced self-rated health (Nummela et al. 2011), and increased mortality (Steptoe et al. 2013) in older people. The risk of suicide increases in older people who are lonely and depressed (Koponen et al. 2007). In England, local authorities are expected to monitor loneliness in older people as part of the Adults Social Care Outcomes Framework (DoH 2012) as it is seen as a major threat to health.

18.5 Social Capital and Loneliness in Older People: A European Context

For the purpose of this chapter, we ran a series of analyses based on the European Social Survey (ESS) data from year 2010. The main aim of the ESS is to provide high quality data over time about behavior patterns, attitudes, and values of Europe's various populations. It consists of an effective sample size of 1,500 face-to-face interviews per country obtained by using random probability methods.[2]

Here we restrict the analyses to Finland, Poland, and Spain and to people aged 50 and over.[3] These countries represent three different welfare regime types (Esping-Andersen 1990; Ferrera 1996; Rostila 2013) that differ with regard to their institutional characteristics. Finland has often been categorized as member of the "universal" or "social democratic welfare state," whereas Poland and Spain can be said to be part of the "post-socialist" and "Mediterranean" welfare systems, respectively. The universal welfare state is characterized by higher levels of welfare provisions mainly based on universal social benefits, compared with the Mediterranean welfare regime with lower levels of social protection and the post-socialist regimes with a rather developed social security system with, however, low benefits.

We used these countries to study the association between social capital and health among older people in order to assess (1) if social capital and loneliness varies between the countries and (2) if loneliness consequences of structural and cognitive aspects of social capital vary. We used correlation and logistic regression analyses. Design weights were applied to the values presented in the tables.

From the ESS we selected social contacts, i.e., structural social capital, through the question: "how often do you meet socially with friends, relatives or work colleagues?" The response alternatives were "low" (never, less than once a month), "moderate" (once a month, several times a month), and "high" (once a week, several times a week, every day). Interpersonal trust or the cognitive aspect of social capital was measured with the question: "would you say that most people can be trusted, or that you cannot be too careful when dealing with people?" The original response categories, which ranged from 0 (you cannot be too careful) to 10 (most people can be trusted) were divided into three: low (0–3), moderate (4–7), and high (7–10) trust.

Loneliness was used as an outcome variable and was measured with the question: "how much of the time during past week you felt lonely?" The response alternatives were "none or almost none of the time," "some of the time," "most of the time," and "almost all of the time." The response alternatives "most of the time" and "almost all of the time" were collapsed into one category in Table 18.1.

The analyses were also adjusted for relevant sociodemographic variables such as gender, education, marital status, and income. Marital status included the

[2] For further details of ESS sampling methodology and survey design, see http://www.europeansocialsurvey.org/.

[3] These countries have also been analyzed within the COURAGE in Europe project (http://www.courageproject.eu/).

Table 18.1 Distribution (%) of socio-demographic indicators, social capital indicators, and loneliness by country

	Finland	Poland	Spain
	$N=944$	$N=734$	$N=752$
Gender			
Men	51.8	55.6	54.1
Women	48.2	44.4	45.9
Age			
50–64	53.6	61.3	53.8
65+	46.4	38.7	46.2
Marital status			
In a relationship	64.7	64.6	69.7
Single	35.3	35.4	30.3
Educational level			
Primary	41.1	55.3	74.4
Secondary	24.3	26.9	7.8
Tertiary	34.5	17.8	17.8
Income			
Coping on income	87.2	59.9	75.5
Not coping	12.8	40.1	24.5
Social contacts			
Low	6.4	23.5	8.6
Moderate	31.5	46.4	19.5
High	62.1	30.1	71.8
Interpersonal trust			
Low	8.6	41.3	24.9
Moderate	55.5	46.6	65.7
High	35.9	12.1	9.4
Experienced loneliness			
All or almost all of the time	4.0	14.9	10.3
Some of the time	20.1	20.6	29.0
None or almost none of the time	75.9	64.5	60.7

Source: European Social Survey, 2010, weighted data

response alternatives: "in a relationship" (legally married, in a legally registered civil union), and "single" ("separated," "widowed/civil partner died," and "none of these"). Education was measured with a question about the highest level of education achieved and included three categories: primary (less than lower secondary; lower secondary), secondary (upper secondary, post-secondary), and tertiary (lower and higher tertiary). Income was assessed with feeling about current household income and the original response alternatives were divided into two: "coping on income" (living comfortably on present income, coping on present income) and "not coping on income" (difficult on present income, very difficult on present income). The analyses were also adjusted for gender and two age groups, 50–64 and 65 years and over.

18.5.1 Social Capital and Loneliness in Finland, Poland, and Spain

Table 18.1 suggests differences between Finland, Poland, and Spain when it comes to informal social contacts and trust. High social contact was found in 62 % of the Finnish sample and 72 % of the Spanish, whereas only 30 % in the Polish. High trust was also found in Finland (36 %). In contrast, the rates of low trust were high in Poland (41 %) as well as Spain (25 %). The findings corroborate previous research suggesting that the level of social capital in terms of contacts and trust is high in northern European countries (van Oorschot 2006; Rostila 2013) and that older people from the Mediterranean countries have larger family networks and social contacts than other European countries (Litwin 2010). On the other hand, studies suggest that post-socialist countries such as Poland experience lower levels of social capital (see Rostila 2013), which was also found here. The reason why the northern European countries, including Finland, repeatedly score high on social capital is not fully understood. However, it has been suggested that high level of social equality in the Scandinavian countries reduces social capital inequalities on a national level (Kumlin and Rothstein 2005; Pichler and Wallace 2007). In other words, when inequality increases, trust and social participation decreases.

The loneliness pattern follows a divide that has been seen in other studies (Sundström et al. 2009; Yang and Victor 2011), so that older people in northern Europe report lower levels of loneliness than those in southern Europe such as Spain. The highest levels of loneliness were, however, found in Poland. It has been suggested that the value systems and ideology of individualism in the Scandinavian countries may lower the levels of experienced loneliness. While living alone is more typical in northern Europe, feelings of loneliness are also lower as compared to the more collectivistic societies of southern Europe (Jylhä and Jokela 1990). In the next analyses, experienced loneliness is dichotomized into lonely (all or almost all of the time; some of the time) and not lonely (none or almost none of the time). We analyzed the likelihood of not being lonely rather than being lonely.

The results in Table 18.2 show that the distribution by loneliness varied among older people in Finland, Poland, and Spain with respect to social contacts. Interestingly, in Poland, older people with moderate social contacts showed less loneliness as opposed to the high social contact groups in Finland and Spain. Significant differences in loneliness were found in Poland in terms of interpersonal trust so that the absence of loneliness was more commonly reported in high trusting respondents.

Finally, Table 18.3 shows the association between social capital and loneliness in Finland, Poland, and Spain, respectively, when controlling for different background variables. Older people with high social contacts were more likely to report the absence of loneliness in Finland and Spain when compared to those with low social contacts, although this was not seen in Poland. The results also reveal a positive correlation between moderate trust and loneliness in the Polish sample, however not in the Spanish or Finnish samples. The empirical findings thus suggest an association between social capital and loneliness among older people in Finland, Poland, and Spain.

Table 18.2 The prevalence (%) of the absence of loneliness by country and the social capital variables

	Finland	Poland	Spain
	$n=712$	$n=463$	$n=459$
Social contacts			
Low	63.3	56.8	47.7
Moderate	75.3	70.2	57.1
High	77.5	62.1	63.7
p	0.049	0.008	0.024
Interpersonal trust			
Low	74.1	56.6	56.1
Moderate	74.4	69.6	61.8
High	78.5	71.3	68.6
p	0.304	0.001	0.159

Source: European Social Survey, 2010, weighted data
Note: Absence of loneliness (none or almost none of the time)

Table 18.3 Odds ratios (OR) and 95 % confidence intervals (CI) for the absence of loneliness in Finland, Poland, and Spain

	Finland		Poland		Spain	
	OR[a]	(95 % CI)	OR[a]	(95 % CI)	OR[a]	(95 % CI)
Gender: male	0.91	(0.65–1.28)	1.11	(0.91–1.89)	1.38	(0.99–1.92)
Age group: 50–64	0.99	(0.70–1.40)	1.31	(0.91–1.89)	0.89	(0.64–1.25)
Marital status: in a relationship	**3.41**	(2.44–4.80)	**4.02**	(2.75–5.86)	**4.51**	(3.16–6.44)
Education						
Secondary	1.27	(0.84–1.92)	0.87	(0.58–1.33)	1.02	(0.55–1.87)
Tertiary	**1.63**	(1.09–2.42)	1.27	(0.75–2.17)	1.24	(0.79–1.94)
Income: coping on income	**2.64**	(1.71–4.06)	**2.47**	(1.71–3.57)	1.38	(0.95–2.01)
Social contacts						
Moderate	1.82	(0.97–3.44)	1.37	(0.89–2.13)	1.23	(0.66–2.31)
High	**2.29**	(1.24–4.22)	1.07	(0.67–1.71)	**1.88**	(1.08–3.28)
Interpersonal trust						
Moderate	0.71	(0.40–1.28)	**1.60**	(1.11–2.32)	1.05	(0.72–1.53)
High	0.71	(0.49–1.66)	1.72	(0.95–3.12)	1.45	(0.77–2.73)
Valid *N*	934		712		732	
2 log Likelihood	920.33		769.415		893.608	
Cox & Snell R^2	0.110		0.190		0.135	
Nagelkerke R^2	0.165		0.262		0.183	

Source: European Social Survey, 2010, weighted data
Note: A *bold* figure indicates a statistically significant difference ($p<0.05$); Reference categories: gender "female"; age group "65+"; marital status "single"; education "primary"; income "not coping"; social contacts "low"; interpersonal trust "low"; absence of loneliness (none or almost none of the time)

However, the association differs between the countries whether structural or cognitive aspects of the concept were analyzed, implying that the meaning of social capital for loneliness and well-being may vary depending on the society in which one lives.

Before we conclude and discuss the ability of social capital to promote well-being in older people, it is important to note some limitations with our analyses based on the ESS data. We included only three European countries here to illustrate differences in social capital and loneliness between older people in Europe. Although more countries are preferable, our results are in line with previous research on social capital and health and well-being based on more European countries (Poortinga 2006; van Oorschot 2006; Yang and Victor 2011). In order to understand how much of the differences in loneliness can be explained by differences among individuals and how much of the variation stems from differences among the countries, different types of statistical analyses are needed such as fixed effect analyses or multilevel analyses.

Further, responses to loneliness may be sensitive to cultural environment, and different nationalities may interpret questions on well-being differently. Given the cross-sectional design of the data, we cannot draw conclusions about causality. We assume that social capital has a positive influence on the absence of loneliness, although a reversed causality is also likely. We did not control for health status in our analyses. Older people with good health may remain socially active and more trustful because of their good health status, which may influence the level of loneliness. Finally, the measure of social capital is not fully validated, although similar types of indicators have been used previously (e.g., Islam et al. 2006).

18.6 Discussion and Conclusions

This chapter started with an overview of the concepts of social capital, mental well-being, and loneliness. The impact of social capital on loneliness was highlighted by analyzing ESS data for Finland, Poland, and Spain. In this final discussion, we acknowledge that social capital offers a way to insert a social aspect into debates on active and healthy ageing for various groups of older people.

Social capital has attracted interest in both policy and academic literature because it has been recognized that the quality of social relationships contributes to health and well-being. An important aspect of the study of social capital is its dual focus on individual as well as collective features, suggesting that social capital can be used as an individual resource to reach personal goals such as access to emotional support, resources, and well-being. In addition, social capital can be seen as a collectively produced resource that is generated within a neighborhood, community, or society to advance collective welfare of society. This suggests that interventions to strengthen social capital need to focus on both access to resources within social networks (e.g., bring together groups normally divided along age, ethnicity, gender) as well as macro-level social and health policies (e.g., facilitate the development on nongovernmental organizations) (see WHO 2004).

In this chapter we focused on the absence of loneliness that is theoretically linked to mental well-being as a positive aspect of mental health rather than negative aspects such as mental disorders and depression. Loneliness is related to reduced quality of life, depressive symptoms, cognitive decline and increased mortality, and policies which aim to reduce loneliness are important for public health. Our chapter underscored that social capital has health beneficial qualities but that the meaning of social capital for well-being could differ depending on welfare state context, an issue that has been extensively discussed in relation to self-rated health (Rostila 2013). A recent systematic review showed that social capital has been associated with various mental well-being outcomes among older people (Nyqvist et al. 2013b). However, to date, research has failed to assess the relationship within a broader institutional or political context such as welfare state regimes. Our initial analyses in this chapter, showing social capital as well as loneliness differences between European countries, suggest that this is an issue that should be more thoroughly investigated in the future.

Active ageing is not only a matter of "productive ageing" and working longer, it is also, as we have seen in this chapter, a matter of social inclusion, participation, trust, and engagement which tend to have health beneficial qualities. Interventions that enhance health and mental well-being in the wider older population are important if social policy objectives of healthy ageing are to be accomplished. An important part of achieving active and healthy ageing is ensuring equality regarding social capital resources. Within health research much focus has been on establishing the association between social capital and health. Social capital is, however, an unevenly distributed resource between groups of older people (e.g., urban–rural older people; older people living at home or in institutional settings (Nyqvist et al. 2013a)) or even between nations, as seen in this chapter. The best-known consequences of social capital are health and well-being. There are far fewer propositions on how to generate social capital. For example, human capital such as education and skills is correlated with social capital, and policies focusing on education and training could also generate social capital and influence the level of well-being. In the literature, there is an emerging consensus that the welfare state could stimulate social capital (Rostila 2013), so that more welfare investment contributes to the social capital of the inhabitants. In countries with higher levels of welfare provisions, older people supposedly will have the time (due to retirement policies) and financial resources (due to welfare support and pensions) to actively take part in organizational activities and to socially connect with family, friends, and neighbors.

To conclude, the findings from this chapter suggest that there are differences in social capital and loneliness between older people living in Finland, Poland, and Spain. The level of loneliness tends to be lower with higher levels of social capital, although this association differed between the studied countries. Social capital as a resource can operate at different levels (micro, meso, and macro) as a promoting factor for health and well-being. The focus throughout the chapter has been on older people, who constitute a very heterogeneous group with regard to health, economic resources, age, gender, living environment, and social capital, and these differences need to be acknowledged when strengthening active and healthy ageing.

Based on the findings presented in this chapter, we conclude that social capital cannot be overlooked in research or by policymakers when considering different ways of improving well-being for various groups of older people in Europe.

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Chapter 19
Reading Metres: Vision, Instrumentation and Evaluation in Voluntary Post-licence Training for Older Drivers

Mirka Rauniomaa, Eric Laurier, and Heikki Summala

19.1 Introduction

A key concern in maintaining an active, autonomous lifestyle through adulthood and into old age is out-of-home mobility, that is the possibility for individuals to move and participate in activities outside their immediate home environment (Holland et al. 2005; Mollenkopf et al. 2002; Siren and Hakamies-Blomqvist 2009; Webber et al. 2010). Out-of-home mobility contributes to the overall well-being of senior citizens, benefitting them physically, psychologically as well as socially. Transport makes out-of-home mobility possible by providing access to goods, services, people and places, and it enables both 'serious' travel that addresses a distinct need, such as running errands, and 'discretionary' travel that generates enjoyment, such as spontaneous outings with friends (Davey 2007). Furthermore, it is not only journeys that are actually undertaken but also 'potential travel' that shapes out-of-home mobility:

Dr. Rauniomaa and Dr. Laurier are responsible for identifying the phenomenon, analysing the data extracts and writing the chapter. Prof. Summala and his research team collected the data and prepared them for analysis. Prof. Summala also complemented analyses of the video data with observations from additional research material.

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knowledge about being able to travel on a whim or out of acute necessity contributes to how mobile senior citizens consider themselves to be (Metz 2000).

Private car travel constitutes an increasingly significant mode of transport for senior citizens, with the amount of older licenced car owners generally on the rise and the current transportation infrastructure geared heavily towards this means of mobility (Alsnih and Hensher 2003; Bartley and O'Neill 2010). While private car travel gives senior citizens opportunities to continue leading mobile lives and thus to sustain their well-being, it may at the same time pose them various challenges. Gandolfi (2010) identifies three types of age-related decline that older drivers may suffer: (1) physical (e.g. restricted movement of head and neck, causing difficulties in scanning the road environment), (2) cognitive (e.g. trouble in processing information, causing slower reactions) and (3) visual (e.g. problems with sight, causing hitches in reading road signage and markings). Older drivers who are affected by such impairments have been found to cope with them by means of self-regulation, i.e. by reducing driving or avoiding specific driving situations (Raitanen et al. 2003; Charlton et al. 2006; Molnar et al. 2013), or, as a more drastic alternative, to cease driving altogether (Adler and Rottunda 2006; Musselwhite and Shergold 2013). While they generally show good self-judgement of changes in their driving skills and have good ability to adapt to those changes, older drivers, and women in particular, may lack confidence as drivers and would often benefit from additional training (Musselwhite and Haddad 2010; Siren and Meng 2013). Indeed, it has been suggested that post-licence driver education could provide more opportunities to practice driving, to self-reflect on one's skills as well as to interact with others in an environment where one feels safe to express one's views (Hatakka et al. 2002; Nasvadi 2007).

In this chapter, we shall examine how older drivers may themselves take up and deal with potential age-related challenges as they drive in real traffic in real time. We shall step into a car, so to speak, with an older driver for a fragment of a journey and explore how a potential problem in the driving activity emerges; how it is used as a basis for instruction on the one hand, and for self-reflection on the other; and how old age as a category is first evoked and then dismissed in interaction. The chapter draws on ethnomethodological conversation analysis (EMCA) and on audio and video recordings of voluntary post-licence training for older drivers.

19.2 Data and Method

The data used in the study were collected by Prof. Heikki Summala and his research team (Esko Lehtonen, Isa Dahlström, Harri Hiltunen, Jarkko Hietamäki and Jami Pekkanen) in the Traffic Research Unit at the University of Helsinki, Finland, in 2010. The data consist of voluntary post-licence training sessions for older drivers and include video recordings that capture the vocal and bodily conduct of participants inside a car. Additionally, eye recordings and car telemetry data of the sessions are available. The drivers are women between 59 and 70 years of age who, at the time of data collection, had a valid driving licence but who had not driven a car for a long time and had little driving experience overall. The training included three 1-h driving sessions in real traffic

in real time. During the sessions, the drivers were assigned various tasks that were aimed at the drivers gaining practice in driving and the instructors gaining information to evaluate, and eventually to help the drivers improve, the performance. The drivers gave their informed consent for the use of the data for research purposes. For a description of the data collection process (in Finnish), see Summala et al. (2011).

The video recordings include instances where drivers explicitly refer to challenges that they face in driving or handling the vehicle: these concern different visual and physical impairments (see Gandolfi 2010), such as difficulties in seeing metres on the dashboard and traffic signs in the surrounding environment or trouble in positioning oneself appropriately inside the car and turning to look at relevant other road users. The challenges are often presented by the driver, and treated by the instructor, as possibly age related and as potentially problematic in terms of the ongoing driving activity. For this chapter, we have selected one such case to explore in close detail.

In examining references to possibly age-related challenges in the data and in presenting the particular case at hand, we draw on EMCA. Based on this approach, we understand human activity and interaction to rely on the categories that members of society or a particular community use to recognise the actions of others and produce their own actions as recognisable (see Francis and Hester 2004; Garfinkel 1984 [1967]; Ryave and Schenkein 1974). Furthermore, we are interested in sequences of interaction where the design and timing of a vocal or embodied action builds on what has occurred immediately before and, in turn, impacts on what comes next (see Heritage 1984; Schegloff 2007). In this way, we aim to uncover the practices and resources through which participants construct the meaning and order of their everyday conduct on a moment-by-moment basis. Potential age-related challenges, for example, are examined as they gradually become manifest in participants' talk and other conduct and as participants in this way evidently orient to them in social interaction.

A classic problem in EMCA studies is that of 'omni-relevant' categories such as doctor and patient during a medical consultation or teacher and student in an instructional setting. While these categories are always potentially relevant, finding where the parties to the activity actually do orient towards them or draw upon them as a resource is harder to establish. In the case of older drivers taking driving lessons during a research project, there are anyway an even more challenging number of seemingly omni-relevant categories: older person being the one that is the concern of this book, but also driver and passenger, instructor and pupil, researcher and participant. A number of these converge around age in slightly different ways, the study having the relationship between age and driving as its topic but needing to extract information in particular ways. In our analysis of the materials, an abiding problem has been finding any events on the road where age can be disentangled from those other categories, as we shall see in the fragment that follows.

19.3 Vision and Emergent Challenges

The fragment examined in this chapter runs for about 2 min and, as it unfolds, highlights different elements that become relevant during the training, i.e. vision as an ability that may change over time and that can be tested and evaluated, in-car

instrumentation as a resource for interpretation and instruction, and evaluation as a possibility for the instructor to guide and the driver to self-reflect. The fragment involves four participants: at the front, the older driver-pupil behind the wheel and the instructor beside her, and, at the back, a researcher who is in control of data collection and another instructor who here acts solely as an expert observer. It is the second day of training for this particular driver, and she is following a specific route under the instructor's guidance. The fragment is presented as transcripts and framegrabs, which have been edited in order to protect the anonymity of the participants. In the transcripts, RES refers to the researcher, DRI to the driver and INS to the instructor at the front (see Appendix for other transcription conventions). The location of the framegrabs in relation to the transcripts are indicated with asterisks (*) and plus signs (+).

19.3.1 Setting Up a Test and Revealing a Potential Problem

The fragment begins some 20 min into the training session when the driver has just entered a carriageway with multiple lanes. In the first extract, the researcher sets up the situation as a test by requesting the driver to read the milometer on the dashboard (lines 01–03), which involves the driver's having to shift her gaze from the roadway to relevant instrumentation on the dashboard in the near space and thus touches on issues of vision.

01 RES: kertoisitteko mulle että,
could you please tell me,
02 *kuinka monta +kilometriä tällä autolla on ajetettu- (.) ajettu,
how many kilometres this car has been drivenen- driven,
03 että mitä se mittari< (1.0) matkamittari näyttää.
that what does the meter< milometer show.
04 DRI: °ootappa nyt°, kuustuhatta neljääsataa viis.
°hang on now°, six thousand four hundred five.
05 RES: joo. kiitos.
yes. thanks.

The researcher makes the request in order to glean information that can later be used to assess the driver's multitasking performance: the driver is deliberately put in a situation where she has to control the car, take notice of relevant events taking place outside the car and the request is also then asking her to attend to a single detail inside the car, namely a figure displayed in the milometer on the dashboard. Requests, as an action produced through talk, are designed so as to make relevant a particular type of response: typically, if a response is not provided right away, the delay is

Fig. 19.1 Driver turns her gaze from roadway to dashboard (*arrows*); framegrabs taken at points when researcher begins to utter 'kuinka' (*asterisk*) and 'kilometriä' (*plus sign*)

analysable—or, if a response is not produced at all, that is also analysable as, for instance, a refusal or a failure (Schegloff 1968; Schegloff and Sacks 1973; Rauniomaa and Keisanen 2012; Stivers and Rossano 2010). In this case, the request is being used with the expectation that with an older driver it can be used to measure how the driver manages multitasking, especially as it involves alternating between looking near and far while driving (Wikman and Summala 2005). We can note that she is not being asked to read the speedometer, despite that being the more commonly used instrument in driving practices, but another relatively standardised instrument that requires similar focusing on details inside the car. In this context, reading the milometer has the additional value of distancing the driver from the information that she is asked to provide: a key piece of information car owners—rather than drivers—are expected to know is the mileage of their car because this number indexes cycles of car servicing, parts replacement, financial value and eventual sale or scrapping. For on-road driving performance, reading the milometer is not relevant at all. In a sense, then, the car itself here serves as an instrument for investigating the capacities of the driver because it is unfamiliar to her and, like an optometrist's consultation room (Gibson et al. 2011), has previously unseen optical characters for her.

The driver in this fragment does then orient to the relevance of an immediate response and the test that has been set up: she turns her gaze towards the dashboard to look for the requested mileage on the milometer when the researcher's comment is still under way but already recognisable as a request for information (Fig. 19.1) and continues to glance at the milometer during her response.

Vision thus becomes a relevant ability that the driver is to draw on in this test setting. The driver also inserts a counter-request, *ootappa nyt* 'hang on now' (line 04), which serves as a preface to an eventual compliance and buys the driver more time to provide the actual answer. During her request for time, the driver continues glancing at the milometer and, immediately after the request, she goes on to provide the mileage (line 04). By signalling a slight interactional delay, the driver's response reveals a potential problem with the reading of the milometer, one that may be consequential not in terms of how the driver fares in the multitasking situation but in terms of interaction and participant categories that are invoked through the design and timing of conversational turns.

19.3.2 Evaluating and Giving Advice

The second extract shows how the instructor draws on information available in the instrumentation in front of him, with reference to their present surroundings, to evaluate the driver's performance, and how the driver responds in a subtle but significant way. After the driver has read the milometer (extract 1), 23 s elapse as she drives straight ahead and no one speaks. The instructor can be seen to shift his gaze between traffic ahead and the instrumentation in front of him before he comments on what he has seen (lines 07–09).

06 (23.0)

07 INS: n:yt saavutettiin viimein seitkyt kilometriä tunnissa.
now we finally reached seventy kilometres per hour.

08 .hhh tultiin kiihdytyskaistalta:,
.hhh we came from the acceleration lane:,

09 (2.0) vähän alta kuuttakymppiä. liikenteen sekaan.
at a little under sixty. into the traffic.

10 *(1.0)

11 INS: se on vaan helpompaa jos kiihdyttää heti (siellä).
it is simply easier if one accelerates right away (there).

12 (1.0)

13 DRI: .mt

14 (15.00)

15 INS: jatketaan taas Pasilan suuntaan.
let's continue towards Pasila again.

We can again remind ourselves here of the institutional nature of both the vehicle being used (i.e. a specially adapted car for both training and research), the identities of occupants of the car (e.g. pupil/subject, instructor and researcher) and the ongoing courses of action (e.g. instruction, evaluation and research data collection).

Unlike everyday car travel where the passenger has no instruments in front of them and has to be careful about looking at the driver's instruments at all (Watson 1999), here the instructor constantly monitors instruments, measuring aspects of the driver's performance, such as speed and eye fixations.

In this extract, the instructor evaluates the driver's performance with reference to the current traffic situation, picking up a problem in the speed at which the driver has entered the carriageway this time. He does this as a noticing (see Keisanen 2012) about the present speed of the vehicle, *now we finally reached seventy kilometres per hour* (line 07–09), flagging the problem with the initial temporal marker *nyt* 'now' and the subsequent marker of delay *viimein* 'finally'. The instructor continues by contrasting their present speed, which corresponds to the current speed limit, with their speed on the acceleration lane earlier: *we came from the acceleration lane at a little under sixty into the traffic* (lines 08–09). The evoked contrast implies that the driver has failed to monitor the speedometer, or interpret her sense of speed, and adjust the speed of the vehicle to this specific traffic situation.

It is worth noting that the instructor's noticing uses a formulation of their speed in terms of number (i.e. 70 and 60 km/h), rather than 'fast' or 'slow'. His measure of their speed is obviously taken from his instrumentation, but it is also produced as units of 10 km/h rather than an exact figure (e.g. 61 and 72). What this form of presentation makes relevant is that driving speeds are categorised for different road types rather than in fact the measures the instructor is reading off his instruments as a mere noticing. His noticing is occasioned by the driver reaching each road-type-relevant speed and where she did this. Vision is not brought up explicitly, but it remains an important underrunning theme: monitoring the speed of one's vehicle is key to entering and keeping up with the flow of traffic at different points in time and space.

In response to the instructor's noticing, the driver tilts her head from side to side and puckers her mouth (Fig. 19.2); the driver treats the noticing as containing potential critique, a negative evaluation of her driving. Moreover, the driver's facial expression and head movement can be seen as self-criticism,[1] which in effect shows that the driver has competent knowledge of the driving activity. In other words, although the driver may have failed to pick enough speed on this particular occasion, she shows awareness of what is considered appropriate conduct in traffic, i.e. that the speed of the car should be adjusted with reference to road type and speed of other vehicles, and in line with relevant traffic regulations.

[1] It is worth noting that the driver responds similarly when driving over a speed hump slightly too fast and on other occasions where it is the vehicle, rather than the instructor, that provides feedback about her driving. Furthermore, in arguing that *the driver treats the instructor's noticing as containing potential critique*, we do not wish to present the instructor in any negative light whatsoever. On the contrary, during the first training session on the day before, the instructor gave the driver detailed instructions on how to accelerate on this particular motorway entrance ramp and during this second session, at the beginning of the ramp, he primed her very positively for the task.

Fig. 19.2 Driver puckers her mouth and tilts her head from side to side (*round brackets*); both framegrabs taken at points when a pause in talk occurs (*asterisk*)

Having established that there was a problem in the driving activity, the instructor goes on to give advice to the driver: *it is simply easier if one accelerates right away there* (line 11). The advice-giving builds on and reaches the conclusion of his earlier noticing. It suggests what the driver could do differently on acceleration lanes: it presents accelerating to 70 km/h in the acceleration lane as being the undemanding way of getting into traffic. Therefore, rather than this being a capability problem which the instructor has attributed to the driver, he is presenting her driving as having here taken the more challenging approach to entering a flow of traffic. The problem is thus not to be understood as persistent and unalterable; on the contrary, the instructor has in effect commended the driver's picking enough speed on an acceleration lane earlier (data not shown). However, we also have to maintain the ongoing project here of the 'lesson': the advice-giving is a recognisable instructor's occasioned recommendation that the driver can take home from the situation in order to improve her driving in the future (see Vehviläinen 2010).

19.3.3 Self-reflection

Again, the driver continues to drive ahead and, after driving in silence for almost 30 s, she brings out an issue with her vision. In this third extract, then, the driver begins to deal explicitly with a potential problem that has earlier been revealed but only been alluded to.

16 (28.0)
17 DRI: (mulla on) juuri se että kun,
(I have) exactly the issue that when,
18 (.) lähinäkö (.) on huonontunu ni,
near-sight vision has gotten worse so,
19 mulla on kaksteholasit mutta ku mä en oikein,
I have bifocal spectacles but because I don't really,
20 (.) kauas katsoessa en niitä tarvi:,
looking far I don't need them,
21 ni ei sitte tule,
then I usually don't,
22 *(.) se +että näkee niinku,
to see like,
23 [juuri näen vielä mittarin, ai niin (juu),
I only just see the meter, oh that's right (yes),
24 INS: [°joo°, (.) (se on) ihan vasemmanpuoleista kaistaa,
°yes°, (it is) the lane on the very left,
25 (8.0)

It is here that the driver makes age relevant through self-reflection, a negative assessment of her near-sight vision and 'bifocal spectacles' which are a *category resonant description* (Stokoe 2012), not just for the category of age but of course for the decline of visual capacities in old age: (*I have*) *exactly the issue that when, near-sight vision has gotten worse so, I have bifocal spectacles but because I don't really, looking far I don't need them, then I usually don't* (lines 17–21).

The driver's self-reflection connects back to a prior sequence (extract 1) and accounts both for the interactional delay in providing a reading of the milometer (not to mention the fact that it may have been erroneous) and an understanding of that early request as initiating a test during the driving. Not only does it account for the delay but shows that the driver is aware of her visual difficulties and has taken the appropriate measure by owning bifocal spectacles. At the same time, the driver reasserts that she is a suitable participant in the training by arguing that it is only her near-sight vision that has gotten worse (lines 17–18); after all, being able to drive without spectacles was a recruitment criterion for the participants of the training and research project because spectacles would obstruct relevant research instrumentation from gleaning data. Moreover, the driver suggests that because car-driving involves 'looking far' rather than near, she 'usually' does not have the bifocals on (lines 19–21). As we noted earlier, the central instrument required for driving is the

Fig. 19.3 Driver glances at (*arrows*) and points to (*round brackets*) metres on dashboard; framegrabs taken at points when a micropause in talk occurs (*asterisk*) and when driver begins to utter 'että' (*plus sign*)

speedometer although, as Sacks (1992) observed many decades ago, speed is much more commonly established and assessed by the experienced driver in relation to surrounding traffic.

Although her performance in this training situation does not have any serious repercussions, for instance, so that she could lose her licence, the driver may be treading treacherous ground here: does she have the vision needed in order to drive safely, or not? Is she able to draw on available, relevant resources, such as the speedometer, to judge what is the appropriate speed at each location? She addresses these concerns by glancing at the metres, lifting her hand from the steering wheel to point to them (Fig. 19.3) and noting that she is in effect able to see the metre without spectacles—if 'only just' (lines 22–23). In quite an elaborate way, the driver then conveys that the trouble that she has with her vision may affect her driving performance to a certain extent but is, nonetheless, only minor.

Some of the remedial work done by the driver is, however, overlapped by talk by the instructor, who responds to an earlier part of the driver's verbal contribution, the negative self-assessment. The instructor could here pick up the issue of wearing bifocal spectacles but, instead, he dismisses the driver's account by providing only a minimal response, a quiet *yes*, and then quickly moving on to deal with a more pressing matter, the current traffic situation where the driver should change lanes, by pointing out the lane on the very left (line 24). The driver goes along with the given directions and begins to prepare for a lane change by switching on the indicator. The movement of the car in and through space, at a certain speed, defines when certain actions are timely, so that changing lanes, for instance, is possible and relevant only at certain moments (Haddington 2010; Haddington and Keisanen 2009). When such a moment arrives, dealing with spatial and mobile issues often

overrides any interactional activities: here, too, first the instructor and then the driver dismiss talk about the driver's vision and focus on the lane change.

19.3.4 Small Talk

After the driver has successfully changed lanes, the instructor returns to prior talk. Here, the possibly age-related challenge, the driver's declining near-sight vision, is once more brought up, but in a way that is stripped off of any overtly evaluative quality.

26 INS: ööm:, (.) niin mitenkä päin se oli, nyt<
ehm, so which way was it, now<
27 (2.0) ilman:: silmälaseja ei nää lähelle vai kauas.
without glasses one can't see near or far.
28 DRI: .mt siis en< en näe lähelle ilman laseja.
.mt I mean I can't< I can't see near without glasses.
29 INS: joo,
yes,

The instructor returns to the issue of the driver's vision by requesting clarification: *so which way was it, now<, without glasses one can't see near or far* (lines 26–27). In this way, the instructor treats the driver's earlier self-reflection as relevant and his own direction-giving as interruptive of it. The request for clarification does not specifically highlight the trouble the driver has claimed to have with her vision or the effects it may have on her driving but provides an opportunity for the driver to elaborate on her self-reflection. It is inviting small talk about issues relevant to the present activity and signalling the instructor's newly established availability for such talk, not setting up a new lesson to be learnt for the driver. In response, the driver provides only a brief clarification, *I mean I can't see near without glasses* (line 28), which the instructor receives with a *yes* (line 29). Both participants then fall silent, treating the matter as something that is dealt with to a satisfactory degree and that does not need to be pursued further, as a line of small talk or as anything else.

19.4 Conclusion

With this 2-min fragment of data, we have begun to show how older drivers' performance is assessed through using the car's instruments both as a reading challenge for the driver and a source of 'objective' measures for the instructor and how these are occasioned and made relevant during the ongoing lesson as it

unfolds on the road. We have shown also how it is the driver that introduced an age-related challenge, her declining near-sight vision, rather than the instructors or researcher(s). The relevance of age-related decline in capacities stems, however, from the earlier actions that revealed potential or actual problems, if not quite errors, that relate to driving: the driver is not reading the metres on the dashboard at relevant points in space and time, or at least she does not adjust her driving accordingly.

Matters of both vision and speed relate to what is considered appropriate or inappropriate conduct in traffic. Road users are expected to be able to manoeuvre their vehicles and to abide to speed regulations. In this fragment of data, the driver displays her awareness of both, by accounting with her declining near-sight vision for her failure to follow the speedometer to an adequate degree, and by doing that accounting in a way that does not cast her in an overly negative light. The driver presents the challenge that she faces with her vision as affecting, but not compromising, her driving.

It is worth noting that all the drivers in the study had had a longer break in driving and had relatively little driving experience at the time of data collection. The drivers had therefore not been adapting their driving skills on an ongoing basis to possibly poorer vision and other such age-related decline. In voluntary post-licence training, they are back in the position of reaching a required performance of skills and ongoing competence that will satisfy an instructor, who may not be a gatekeeper advising older drivers for or against driving, but a professional driver nevertheless, representing the highly regulated side of traffic and transport.

That said, we would like to argue that the voluntary and fairly informal nature of the post-licence training that we have examined here is key to the impact that it may have on encouraging older drivers to continue driving as well as to keep up and build up their skills and abilities. Possible age-related challenges may become relevant in older drivers' mistakes and failures when they drive in real traffic in real time. The way in which such mistakes and failures come about and become topicalised in talk also provide opportunities for older drivers to be guided and to self-reflect. When this takes place in a setting where the drivers are evaluated—and are able to evaluate themselves—in order to improve their driving but not, for instance, to renew their licence, older members of society can be seen to receive true support for out-of-home mobility.

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Appendix: List of Transcription Symbols (Based on Jefferson 2004)

wo[rd	onset of overlapping talk
(0.8)	pause in tenths of a second
(.)	micropause, less than 0.2 s
wor-	truncated word
wor<	word ended abruptly but not truncated
hh	outbreath
.hh	inbreath
.mt	smack of the lips at inbreath
°word°	talk softer than surrounding talk
wo::rd	lengthening of a sound
word.	downward intonation
word?	upward intonation
word,	continuing intonation
(word)	uncertain hearing

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Chapter 20
Social Policies for Old Age: A Story of Shifting Images and Time Lag

Kathrin Komp

20.1 Introduction

Population aging pushes aging policies up the political agenda. People now live longer than ever before, and life expectancy is still increasing (United Nations 2009). Moreover, the proportion of older people is increasing across Western countries (Destatis 2011). As a consequence, old age becomes a more prominent part of life, and policy-makers have to pay more attention to it. The attention of policy-makers is further attracted because population aging puts pressure on public budgets, especially those for pensions, health care, and long-term care. Policy-makers need to intervene to balance these budgets and to ensure the sustainability of social provision in times of population aging (Komp and Béland 2012). Additionally, the demographic shift means that electorates are aging, and parties considering the interests of older people might gain more votes in elections (Sinn and Uebelmesser 2002). This combination of financial and strategic considerations puts a twofold pressure on policy-makers to engage with policies for older people.

As populations age, social policies for older people receive additional attention. These policies tackle questions of welfare, social participation, and standard of living in old age (Marshall and Bottomore 1992). They do this, for example, by ensuring the provision of pension benefits and long-term care services. The goal of social policies to address current social problems drives their need for reform in times of population aging. On the one hand, policy-makers need to ensure a sound financial basis for public services to older people (Komp and Béland 2012). This task is challenging, because the growing need for social services for older people coincides with a decreasing number of middle-aged people who contribute to these services financially, and with the ongoing economic crisis which further decreases public budgets. On the other hand, policy-makers need to adapt policies to reflect the

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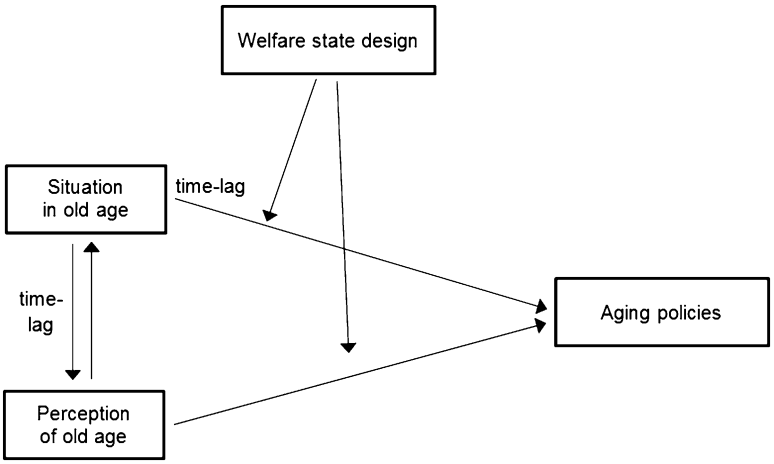


Fig. 20.1 Influences on aging policies

changing character of old age. This changing character arises not only from the increasing number of life-years in poor health at the end of life but also from the increasing number of healthy life-years immediately after retirement (Laslett 1996). This means that older people not only need support in case of frailty but they also have the potential to be active and productive. Policy-makers could strive to tap into this potential to benefit the families and communities of older people. Additionally, today's older people differ from their predecessors in terms of their preferences and life-styles (Gilleard and Higgs 2002), which means that policy-makers need to address them in a different way. Hence, social policies for old age have to be recalibrated as populations age (Komp and Béland 2012).

When we look back at the development of social policies for old age, we can indeed see such recalibrations alongside the progression of population aging. Interestingly, when developing these policies, policy-makers do not only draw on empirical facts as guidelines but they are also guided by their perceptions and images of old age and by the design of the welfare state. Population aging can therefore lead to a range of possible policy reforms (Béland 2005; Komp 2010). Moreover, it takes some time until changes in the lives of older people are reflected in political discourse. Therefore, policy reforms might lag behind changes in the lives of older people (Komp 2010; Riley et al. 1994). This intricate network of influences on aging policies is portrayed in Fig. 20.1.

This chapter takes a closer look at influences on policy-making for old age. It starts by elaborating on the different understandings of old age, based on objective and subjective indicators. It then identifies various influences on aging policies and highlights differences between countries. Next, it explains how time lags cause difficulties in policy-making for old age. Finally, it reflects on the implications of all these considerations.

20.2 Understanding Old Age Through Numbers and Perceptions

There is plenty of debate among both researchers and the public about what it means to be old. When does someone start to be old? What are the characteristics of older people? There is no straightforward answer to these questions, but instead we find multiple opinions, definitions, and understandings, some of which contradict others. The reason is that aging is a multi-faceted, continuous process, and not a state that one reaches between one day and the next. Aging starts at the moment of conception, and continues at varying speeds throughout life. This aging process progresses in different dimensions side-by-side, including physical decline, psychological developments, changing social roles, and an evolving self-image. As a consequence, people understand old age in different ways (Bowling 2008; Komp and Aartsen 2013). The prevailing understanding of old age sets the path for the design of aging policies.

The range of understandings of old age can best be captured in two ideal types. Ideal types are constructs that combine characteristics in a simplified and exaggerated way (Weber 1980). The ideal type that developed first is labeled the "fourth age" or the "old old." It depicts frail old individual who needs help and support. This ideal type was the center of many discussions in the 1970s and 1980s. According to this ideal type, old age starts at the age of 65 years, which is assumed to coincide with retirement and the onset of poor health. From the 1990s, however, the second ideal type of old age became more prominent. This type is labeled the "third age" or the "young old." It portrays old age as a time of good health, activity, and freedom. It emerged alongside the expectation of living a healthy life for longer, and at a time when people started to retire early while receiving generous pension benefits. Both ideal types currently coexist, and a common understanding is that people in their later years transition the third age before they enter the fourth. This means that people typically spend some life-years after retirement in good health, before their health declines and they become frail (Komp 2013; Laslett 1996; Neugarten 1974).

While the interplay between the two ideal types of old age seems clear, the reality is more complex. The ideal types are sometimes hard to distinguish when looking at real people, and there are pronounced differences both within and between countries (Börsch-Supan et al. 2013; Jönson 2013). An additional complication is that the ongoing economic crisis is remolding social structures and pushing lives into new directions. As a consequence, both the lives and image of older people are currently shifting again, although it is still too early to determine what the final outcome of this shift will be (for a more detailed review see Komp 2013). To illustrate the variety of possible understandings of old age, the following paragraphs set out some empirical data. These data reveal that different markers for the onset of old age lead to different results, that facts and perceptions diverge, and that definitions of old age reflect both the past and the social context.

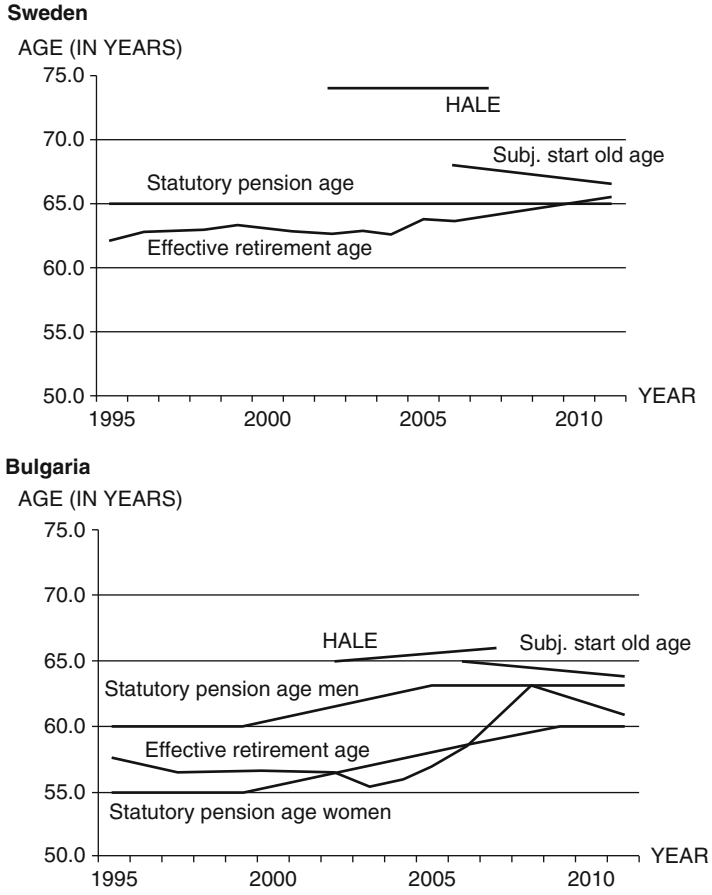


Fig. 20.2 Indicators for the onset of old age, Sweden and Bulgaria 1995–2011. *Note*: *HALE* healthy life expectancy. (*Sources*: European Commission 2012; International Social Security Association 2013a, b; Organisation for Economic Co-operation and Development 2013; own analysis of data of the European Social Survey; World Health Organization 2006, 2009)

Figure 20.2 shows different indicators for the onset of old age in Sweden and Bulgaria between 1995 and 2011. These two countries are very different when it comes to aging. Swedes have the oldest retirement age in Europe and remain healthy the longest after retirement (Komp and Aartsen 2013).

Bulgarians, by contrast, have one of the earliest retirement ages in Europe, and also one of the earliest deteriorations in health (Organisation for Economic Co-operation and Development 2013; World Health Organization 2009). A comparison between Sweden and Bulgaria therefore gives us an impression of the range of situations of older Europeans. The indicators shown in Fig. 20.2 are: the statutory pension age, the effective retirement age, the healthy life expectancy (HALE) (that is, the expected number of years of healthy life, as opposed to total life expectancy),

and the subjective perception of when old age starts. The statutory pension age is the age set out in law as the date of retirement. It is sometimes considered the most important element shaping our understanding of when old age starts (Kohli 1991; Komp 2011). Lately, however, this understanding has been challenged by the fact that people retire earlier, which is shown by the indicator "effective retirement age." Another challenge to the traditional understanding of old age is that people remain healthy for longer, which can be captured by the indicator "healthy life expectancy." Whether or not these facts relate to how the public understands old age can be read from the indicator "subjective perception of when old age starts." This last indicator shows when people think old age starts.

Figure 20.2 reveals that old age can indeed be understood in many different ways. The impactful indicator of the statutory pension age was 65 years in Sweden throughout the period, and increased from 55 to 60 years for Bulgarian women and from 60 to 63 years for Bulgarian men. This indicator has the advantage that it can easily be determined, and the disadvantage that it is ambiguous for two reasons. First, statutory pension ages are not the same for everyone: for example, people in physically demanding occupations have lower statutory pension ages, and from 2001, Swedes had the right to continue working until age 67, if they wished to do so (International Social Security Association 2013b). Second, the values in Bulgaria are gender-specific and they change over time. Compared to the statutory pension age, the effective retirement age gives us a more accurate picture of when people actually retire. It is, therefore, a better depiction of how individuals experience retirement on a personal level, which means that it is relevant for how the public sees the onset of old age. In Sweden, the effective retirement age increased from 62 to 66 years from 1995 to 2011. In Bulgaria, the effective retirement age was more volatile. It was 63 years in 1995, then decreased to 56 years, then increased again to 63 years, and then dropped to 61 years. This volatility, on the one hand, reflects the timeliness of the effective retirement age as a marker for the onset of old age. On the other hand, it also renders this indicator a challenging choice for comparisons over time. By comparison, the HALE is more stable over time. It was 74 years in Sweden between 2002 and 2007, and increased from 65 to 66 years in Bulgaria over the same time period. This indicator for old age is interesting for researchers studying life-phases and the changing structure of later life. Life-phases are longer lasting situations within a person's life that center on specific activities. Old age was for a long time understood as a life-phase that started with retirement and centered on coping with declining health. However, because of early retirement and an increasing HALE, this definition no longer holds true. Therefore, some researchers suggested splitting old age into two consecutive life-phases: the third and fourth ages. Some researchers argue that the third age contrasts so drastically with the traditional understanding of old age that it could be seen as an extension of mid-life instead of a first period of old age (Komp 2013). Following this argument, the HALE signals the onset of old age as a period of frailty in later life.

The fourth indicator shows at what age individuals perceive old age to start. It therefore shifts attention away from objective measures and instead focuses on the subjective dimension. Swedes pinpointed the subjective onset of old age at 68 years

in 2006 and 67 years in 2011, whereas Bulgarians identified it as 65 years in 2006 and 64 years in 2011. The subjective start of old age is therefore later than both the statutory pension age and effective retirement age, and earlier than the HALE in both countries. In addition, all indicators for the onset of old age point to later ages in Sweden than in Bulgaria.

These data show that old age can be understood in many different ways, that these understandings change over time, and that they differ between countries. The information also shows that there is a gap between objective facts and perceptions, despite these being interrelated. One reason for this gap is a time lag, which will be discussed later in this chapter. An important implication for policy-makers is that they need to reflect on their own understanding of old age when designing aging policies (Komp and Béland 2012). Such a reflection will help them to filter the information relevant to them out of the broad debates on old age. It will also help them to communicate the reasoning behind their policies to the public and to other bodies of government. A second implication is that policy-makers need to address both facts and perceptions when designing aging policies. While objective facts seem a sound basis for the design and implementation of political intervention, subjective perceptions play a big role in how the electorate reacts to political intervention and policy reforms (Kohli 1991). Policies that are factually justified but perceived as unjust can meet resistance, whether in the form of protests or as losses at elections. Policy-makers, therefore, need to consider both objective and subjective aspects, when designing aging policies.

20.3 Aging Policies at the Crossroads Between Facts and Images

Aging policies demand a balance between facts and perceptions, but these are not the only demands on them. Policy-makers do not act in a vacuum, but are embedded in society. This means that society shapes the logic with which policy-makers approach older people, and policies therefore have to be concordant with society to be accepted (Edmondson 2013). The aspects of society that are particularly important for aging policies are the overall social structure, culture, values, and the design of the welfare state. These aspects culminate in two images that are major signposts for aging policies: one of old age, and the other of a "good society" (Esping-Andersen 2003). The image of old age combines the perceptions of when old age starts with further ideas and perceptions, for example, on the situation of older people and their activities, to obtain a multidimensional picture of older people (Edmondson 2013). The image of a good society combines ideas on how a society should ideally be structured and how such a structure can best be obtained. It therefore captures the logic guiding the design of welfare states and of social policies (Esping-Andersen 2003). Esping-Andersen (1990) suggested that these ideas of a good society can be captured in distinctive ideal types of welfare states, which he coined "welfare regimes." When we view both the shifting images of old age and

the different welfare regimes, we see a broad range of frameworks for aging policies unfolding. These frameworks differ over time and between countries.

The shifting image of old age created three major strands of aging policies. The first strand is the earliest one, addressing older people as frail individuals in need of support (*fourth-agers*). It is based on the idea that people become old once they retire, and that their health and capacities for self-support decline from that time on. Consequently, policies of this kind try to make up for losses experienced by older people, and include, for example, pension policies to compensate for a loss of income, and healthcare services to address declining health. It was this kind of aging policy that sparked the discourse about population aging as a burden on welfare states, because it stressed the increasing need for support that an aging population might bring (Johnson et al. 1989; Komp and Béland 2012). The second strand of aging policies entered the scene during the 1990s, supplementing the aging policies already in place. This strand addressed a new cohort, meaning people who were born at a later date. This new cohort of older people has a longer HALE than its predecessor, and gave rise to the ideal type of the healthy "third ager" bringing new possibilities to society and to the welfare state. This new kind of aging policy underlines that paid work is not the only productive activity, and that other activities such as volunteering in organizations, grandparental childcare, and care-giving to kin also constitute valuable contributions to society and the welfare state (Morris and Caro 1997; Morrow-Howell et al. 2001). If older people engage in these activities, they might address social needs that publicly funded health and social care services would otherwise have to meet. These policies also try to strengthen the engagement of older people in such activities, primarily through increasing the mandatory retirement age and by encouraging older people to volunteer. In this way, they hope to give population aging a positive spin for the economy and for public budgets, which dampens the burden-centered discourse (Komp and Béland 2012). The third strand of aging policies emphasizes the idea that older people are individuals who should not primarily be categorized according to their age. Instead, individuals move through the different age-groups throughout their lives, and their situation has to be viewed from a longitudinal perspective. Therefore, this perspective, which started to gain momentum at the beginning of the twenty-first century, suggested that policies pay attention to life course effects (Esping-Andersen et al. 2003; Morel et al. 2012). The life course spans all life-years from cradle to grave, and it is characterized by an individual's activities and experiences within that time (Grenier 2012). Proponents of life course effects argue that individuals' experiences can have long-term effects, which influence the further progression of their life course, even years or decades into the future (Elder 1994). The education people receive during their youth, for example, can influence how working careers progress, and at what age people retire from work (Gouldner 2001). Aging policies that account for such life course effects, therefore, influence individuals during their youth and middle-age in order to achieve effects in old age. These policies intervene at critical periods throughout the entire life course, for example, during periods of unemployment or when health problems occur, and strive to steer the life courses of individuals in the desired direction. Typical goals of such policies are to facilitate the employability of older

people, to help them maintain good health for longer, and to ensure that people accumulate enough pension rights during their working careers to receive reasonable old age pensions (Komp and Marier forthcoming). Taken together, these three strands changed approaches and priorities of aging policies over time.

Country-differences between aging policies come about because of, for example, the different welfare regimes. These regimes are typically described using three characteristics. The first characteristic is stratification, meaning the degree and kind of social inequalities it produces. The second characteristic is de-commodification, which describes the degree to which welfare provision allows individuals to shed their role as a commodity in the labor market at times of, for example, poor health. The third and final characteristic is the welfare mix, which means whether governments assign the responsibility for welfare provision to the market, the family, or the state (Esping-Andersen 1990). Esping-Andersen (1990) originally described three welfare regimes. The first regime is the social-democratic one, which is typical of Northern Europe. It favors strong state intervention that reduces social inequalities and allows individuals to maintain a decent standard of living even when they have to temporarily leave the labor market, for example, for health reasons or because of unemployment. The second regime is labeled as liberal, and it prevails in Anglo-Saxon countries. It strongly relies on the regulatory mechanism of the market, stresses the individual's role as a commodity in the labor market, and accepts the resulting social inequalities. The third regime is described as conservative, and it is common in continental Europe. It uses a mix of state and family responsibility for ensuring the citizens' well-being, its social insurances create social inequalities along occupations, and it allows people to maintain a livelihood when they cannot work (Esping-Andersen 1990). Scholars such as Ferrera (1996) and Leibfried (1992) added a fourth regime capturing the situation of Southern European countries to this typology, and they labeled it as rudimentary. This regime recognizes the family as the main player in welfare production, it reduces social inequalities only to some extent, and it provides only little protection against the risks of not being able to engage in paid work. Finally, there are currently discussions on whether Central and Eastern Europe constitutes a fifth, post-paternalistic regime. This regime offers little state protection against the risks of not being able to work, it produces social inequalities mainly between the generations that experienced the communist period and later generations, and it draws on a patchwork of players to provide welfare (see, for example, Aidukaite 2009; Cerami 2006; Fenger 2007). Table 20.1 summarizes each welfare regime according to these characteristics.

Like the design of welfare states, aging and the progression of aging policies can also be described according to the logic of welfare regimes. The countries of the conservative and rudimentary regimes have the oldest populations in Europe, whereas the countries in the post-paternalistic regime have the youngest populations (United Nations 2009). Similarly, the conservative and rudimentary regimes have particularly high numbers, and the post-paternalist regime has particularly low numbers, of third agers. However, people in the social-democratic regime spend a particularly long time in the third age (Komp 2010; Komp and Hoffmeyer-Zlotnik 2012). Countries across all regimes have policies that support frail older people, and

Table 20.1 Welfare state characteristics, old age, and aging policies across welfare regimes

	Welfare regimes				
Examples	Social-democratic	Liberal	Conservative	Rudimentary	Post-paternalistic
Countries	Sweden, Denmark	United Kingdom, Ireland	Germany, France	Spain, Portugal	Poland, Czech Republic
Welfare state					
Stratification	–	+ Income-based	+ Occupation-based	±	+ Generation-based
De-commodification	+	–	±	±	–
Welfare mix	State	Market	State/family	Family	State/family/market
Old age					
Population aging	±	±	+	+	–
Third age	±	±	+	+	–
Aging policies					
Policies supporting older people	+	+	+	+	+
Policies activating older people	+ Mainly work	+ Work and volunteering	+ Work and volunteering	+ Work and care-giving	+ Mainly work
Life course policies	+	±	±	–	–

Aidukaite (2009), Arza and Kohli (2008), Cerami (2006), Esping-Andersen (1990), Ferrera (1996, 2005), Komp (2010), Komp and Hoffmeyer-Zlotnik (2012), Komp and Marier (under contract), Morel et al. (2012)

Note: In this table, + stands for "strong," ± stands for "intermediate," and – stands for "weak"

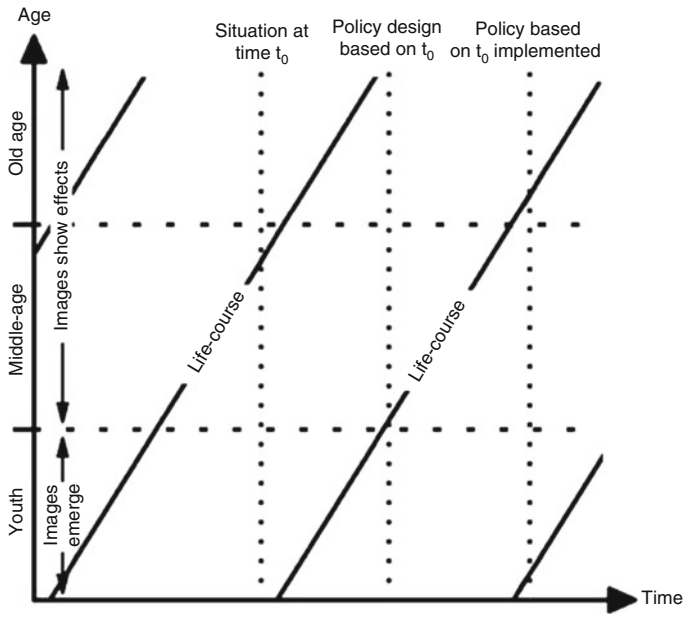
strive to engage healthy older people in the labor market, which usually happens through increases in the retirement age and reforms that block pathways to early retirement (Arza and Kohli 2008). Countries in the conservative and liberal regimes particularly strive to encourage older people to volunteer, and particularly countries in the rudimentary regime recognize and support the role of older people as caregivers to kin (Komp 2010). Life course policies, however, are more unequally developed across welfare regimes. The ideas behind these policies developed particularly early in the social-democratic regime, had gained some standing in the conservative and liberal regimes by the beginning of the twenty-first century, but were still in the background of political agendas in the other regimes at that stage (Komp and Marier forthcoming; Morel et al. 2012). One reason could be that welfare states work with smaller budgets in the rudimentary and post-paternalistic regimes, and therefore needed to wait longer to introduce these new policies.

20.4 The Emergence of Time Lags in Aging Policies

Aging policies are influenced by various factors, such as the situation and image of older people, and the design of the welfare state. However, these factors do not always have immediate effects. Instead, we often see time lags in the making of aging policies. Time lags describe situations with a delay between an event and its effect (Gollob and Reichardt 1987). In policy-making for old age, two kinds of time lags occur: one between the situation and the popular image of older people, and another one between the development of image of older people and the introduction of the policy. Figure 20.3 illustrates both time lags. It positions both time lags in the interplay between historical time and the aging process of individuals. In the figure, historical time is displayed on the horizontal axis, and the aging process on the vertical axis. To make the aging process easier to grasp, the vertical axis is divided into three sections: youth, middle-age, and old age. In this figure, life courses are presented as diagonals. These diagonals signify that life courses represent the aging of individuals while historical time progresses.

The first time lag shown in Fig. 20.3 refers to the influence of images on the activities of individuals. While the foundation for these images is laid during one's youth, one's actions during middle-age and old age still partly depend on them. In other words, one's actions are influenced by images that were prevalent at an earlier date.

Mannheim (1928) explained this time lag through the development process that people undergo as they grow up. During childhood and youth, he argued, people develop a perception of reality, a world view, and their personal way to absorb and categorize new information. These developments then serve as the basis for later activities and decisions. The work of Svallfors (2010) and Goerres (2008) is in line with Mannheim's explanation. They found that preferences for welfare policies and political parties are largely stable over the life course. This time lag has an important implication for aging policies. It entails that young people develop an image of old age, which will change later only with difficulty. Consequently, changes in the



(Goerres 2008; Komp and Johansson forthcoming; Pierson 2004; Riley et al. 1994; Riley and Riley 2000; Svallfors 2010)

Fig. 20.3 The emergence of time lags in aging policies

actual situation of older people might not directly affect the image of older people held by society. Hence, the image and situation of old age might diverge. Older people might therefore find it challenging to forge a new role in society when their situation suddenly changes, as it has, for example, happened because of the economic crisis. It might take a longer period of time, possibly even an entire life-time, for older people to gain this new standing in society. In addition, the time lag entails that policy-makers do not approach policy-making with a blank canvas as a starting point. Instead, they draw on previous images and discussions about old age. Likewise, they have to convince their electorate, which is also influenced by previous images of old age, of the benefits of policies for today's older people. In these situations, the time lag in the effects of images of old age might lead to challenges and tensions, independent of the kind of aging policy chosen (Kohli 1991; Komp and Johansson forthcoming).

The second time lag is inherent in the process of policy-making. It takes a while until a policy becomes effective, and if this processing period is long enough, the original situation might no longer be valid. In Fig. 20.3, this fact is represented by the three vertical lines in the middle of the figure. The first line demarcates the situation at time t_0, which serves as the starting point for aging policies. Once this situation has been documented, it can enter political discussions and influence the policy-making process. Then, after a period, aging policies based on the situation at t_0 might be designed.

This act of designing policies is represented by a second vertical line in the figure. However, the policy-making process is not yet complete at this stage. Instead, it usually takes a while until the newly designed aging policies come into effect. This second delay is partly due to the mode of operation of government bodies, and partly to possible transition periods included in the policies. The time when the policy comes into effect is represented by a third vertical line in the figure. These processes can add up to a period of several years between a situation and the coming into effect of a policy addressing it (Komp and Johansson forthcoming; Pierson 2004). Depending on the speed of social change, the time lag can be unproblematic or it can cause complications. If the social situation changes slowly, as for example, the HALE does (Salomon et al. 2012), the time lag is unproblematic. However, if the social situation changes quickly, as it happened, for example, with the effective retirement age (Organisation for Economic Co-operation and Development 2013), the time lag can cause a problem. In the latter case, the social situation might have changed by the time the policy comes into force, and the policy is already outdated before it has any effect.

20.5 Discussion and Conclusion

Population aging demands a new set of aging policies, and governments developed a range of policies to meet this demand. Some of these policies address older people's need for support, some strive to activate healthy older people, and some frame older people as individuals independent of their age. However, when designing and implementing such policies, a number of challenges arise. One major challenge arises from a possible gap between the situation of older people and the popular image of them. Policy-makers need to address both aspects in their aging policies. Another major challenge arises from time lags that are inherent in the process of policy-making and the effects of images. These time lags underline the importance of the temporal dimension in policy-making (Pierson 2004), and they require precise planning and evaluation steps whenever policies are being designed and implemented. How the influence of images and time lags plays out, however, cannot be generalized, because it is largely specific for countries and periods of time.

The insight in this chapter has implications for active aging policies. Such policies became more common over the past few years, as a reaction to population aging and the increasing HALE. They strive to improve the quality of later life, following the maxim that one should not only add more years to one's life, but also add more life to one's years. Within these policies, "active aging" is understood as the "process of optimizing opportunities for health, participation, and security in order to enhance quality of life as people age. […] The word 'active' refers to continuing participation in social, economic, cultural, spiritual, and civic affairs, not just the ability to be physically active or to participate in the labor force" (World Health Organization 2002, p. 12). Hence, policy-makers have various starting points to

facilitate active aging, and their dedication to this goal became clearly visible when the European Union designated 2012 the "European year for active aging and solidarity between generations" (Eurostat 2011).

Active aging policies can be placed in the overall framework of shifting images and time lag. The growing attention focused on active aging policies indicates that the image of older people as healthy and resourceful individuals is gaining ground. Moreover, it shows that these individuals are considered to possess unstructured time, and that they could increase their activity level. This development marks a first shift in the image of old age (Komp 2013; Moulaert and Biggs 2013). However, the shift is taking place at a time of economic crisis, meaning one of fundamental social restructuring. Because of the economic crisis, older people's financial situation is deteriorating, and they therefore have to work longer, sometimes even beyond retirement age. At the same time, family networks and intergenerational transfers are becoming more important, which means that older people are taking on a more prominent role as providers of grandparental childcare, as care-providers to frail spouses, and as active participants in the household economy (Aartsen et al. 2012). Thus, the lives of older people are changing. There are an increasing number of demands on older people, and older people have to be active in order to ensure their own livelihood and to provide for their family. This development reduces the leeway that older people have in deciding on how to spend their time, and makes them essential pillars for the well-being of their kin. Consequently, the image of older people will probably shift again in the future. However, because of time lags, we are currently drifting into a mismatch between the situation of older people, their image, and the policies addressing them. This mismatch combines a situation of very active and involved older people, an image of heterogeneity between frailty and the potential for activity in old age, and policies that strive to activate older people.

In conclusion, this chapter illustrates the complex background of aging policies. These policies not only need to account for the growing number of older people but they also have to consider the changing character and image of old age and the country-specific welfare state design. When doing this, they have to balance all these aspects and then navigate them through time lags. This challenge gives the process of policy-making for old age its own dynamic and logic. Welfare state responses to population aging must, therefore, not only be based on statistics of demographic change and welfare state expenditures but they also need to consider the qualitative and cultural aspects of aging. Consequently, researchers would benefit from triangulating qualitative and quantitative methods in their studies on aging policies. Moreover, policy-makers addressing aging should keep in mind that they are intervening in matters of culture and traditions at the same time as they are steering social provisions and balancing out public budgets.

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