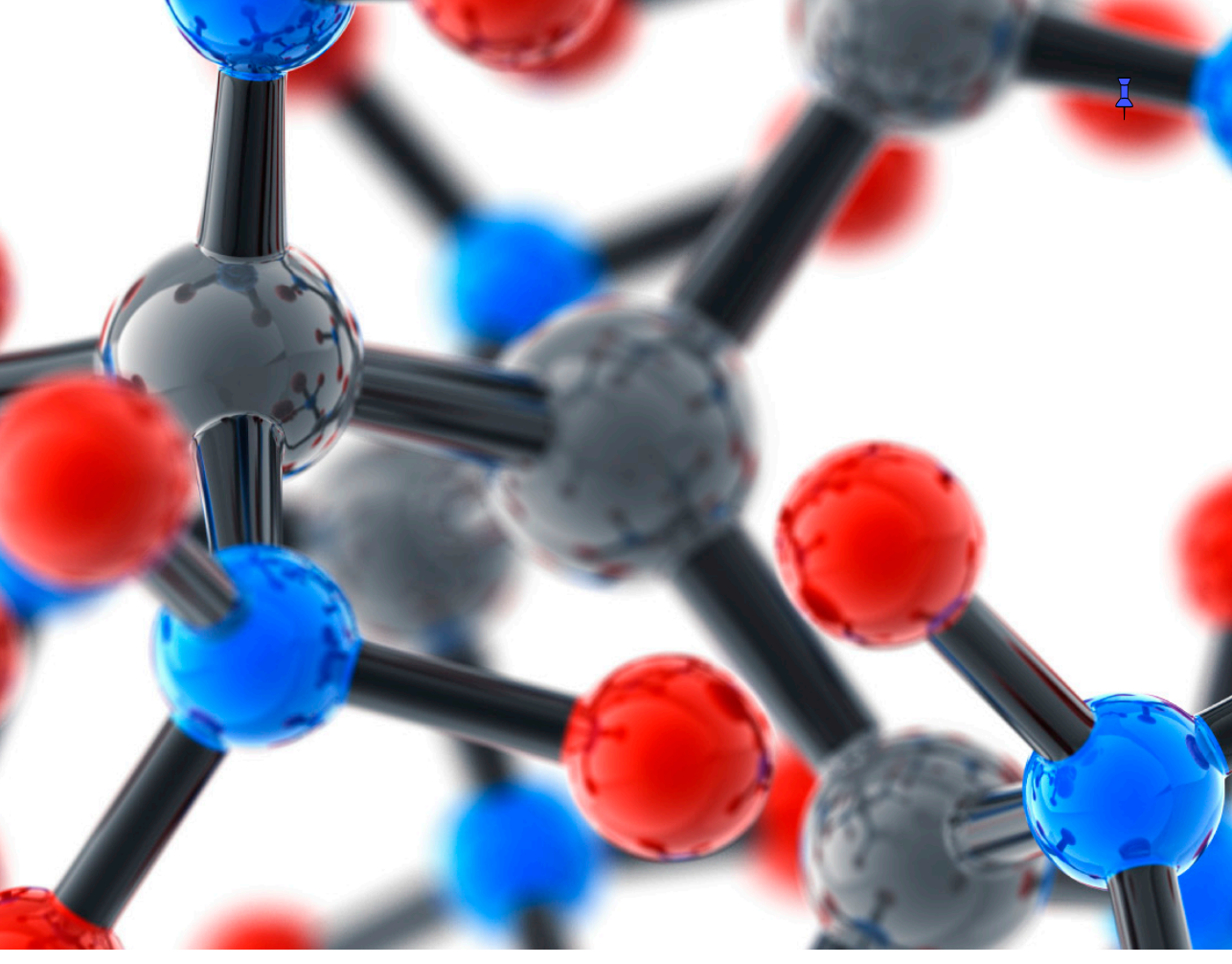

MOLECULAR ASPECTS OF AGING

Understanding Lung Aging

Edited by Mauricio Rojas, Silke Meiners, Claude Jourdan LeSaux

WILEY Blackwell

Molecular Aspects of Aging

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Understanding Lung Aging

Edited by

Mauricio Rojas
Dorothy P. and Richard P. Simmons Center
for Interstitial Lung Diseases;
Division of Pulmonary, Allergy and Critical
Care Medicine;
McGowan Institute for Regenerative Medicine,
University of Pittsburgh School of Medicine,
Pittsburgh, Pennsylvania, USA

Silke Meiners
Comprehensive Pneumology Center (CPC),
University Hospital, Ludwig-Maximilians-University,
Helmholtz Zentrum München;
Member of the German Center for Lung Research (DZL),
Munich, Germany

Claude Jourdan Le Saux
University of Texas Health Science Center, Division of
Cardiology and Pulmonary and Critical Care, San Antonio,
Texas, USA

WILEY Blackwell

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Contributors

Serge Adnot
INSERM U955 and Département de Physiologie-Explorations Fonctionnelles, Hôpital Henri Mondor, Université Paris Est, Paris, France

David E. Bloom
Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, USA

Jorge Boczkowski
INSERM U955 and Département de Physiologie-Explorations Fonctionnelles, Hôpital Henri Mondor, Université Paris Est, Paris, France

Laurent Boyer
INSERM U955 and Département de Physiologie-Explorations Fonctionnelles, Hôpital Henri Mondor, Université Paris Est, Paris, France

Rodrigo T. Calado
University of São Paulo at Ribeirão, Preto Medical School, São Paulo, Brazil

Leena P. Desai
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Alabama Birmingham, Birmingham, Alabama, USA

Deepak A. Deshpande
Pulmonary and Critical Care Medicine Division, University of Maryland School of Medicine, Baltimore, Maryland, USA

George A. Garinis
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas and Department of Biology, University of Crete, Crete, Greece

Francis H.Y. Green
University of Calgary, Calgary, Alberta, Canada

Kevin P. High
Section on Infectious Diseases, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

Anne Hilgendorff
Comprehensive Pneumology Center (CPC), University Hospital, Ludwig-Maximilians University, Helmholtz Zentrum München; Member of the German Center for Lung Research (DZL); Dr. von Haunersches Children's Hospital, Munich, Germany

Anna Ioannidou
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas and Department of Biology, University of Crete, Crete, Greece

Maria G. Kapetanaki
Dorothy P. and Richard P. Simmons Center for Interstitial Lung Diseases, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Ismene Karakasilioti
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas and Department of Biology, University of Crete, Crete, Greece

Jacqueline M. Kruser
Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Claude Jourdan Le Saux
University of Texas Health Science Center, Division of Cardiology and Pulmonary and Critical Care, San Antonio, Texas, USA

Silke Meiners
Comprehensive Pneumology Center (CPC), University Hospital, Ludwig-Maximilians-University, Helmholtz Zentrum München; Member of the German Center for Lung Research (DZL), Munich, Germany

Keith C. Meyer
Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Ana L. Mora
Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Kent E. Pinkerton
Center for Health and the Environment, University of California Davis, Davis, California, USA

Mauricio Rojas
Dorothy P. and Richard P. Simmons Center for Interstitial Lung Diseases; Division of Pulmonary, Allergy and Critical Care Medicine; McGowan Institute for Regenerative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Jesse Roman
Department of Medicine, Division of Pulmonary, Critical Care and Sleep Disorders, Department of Pharmacology & Toxicology, Robley Rex Veterans Affairs Medical Center and University of Louisville, Kentucky, USA

Yan Y. Sanders
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Alabama Birmingham, Birmingham, Alabama, USA

Sinead Shannon
Department of Health and Children, Dublin, Ireland

Pooja Shivshankar
University of Texas Health Science Center, Division of Cardiology and Pulmonary and Critical Care, San Antonio, Texas, USA

Suzette M. Smiley-Jewell
Center for Health and the Environment, University of California Davis, Davis, California, USA

Victor J. Thannickal
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Alabama Birmingham, Birmingham, Alabama, USA

Lei Wang
Center for Health and the Environment, University of California Davis, Davis, California, USA

Mingyi Wang
Intramural Research Program, National Institute on Aging, Baltimore, Maryland, USA

Jingyi Xu
Center for Health and the Environment, University of California Davis, Davis, California, USA; Affiliated Zhongshon Hospital of Dalian University, Dalian, China

Preface

Aging is the inevitable fate of life. It is a natural process characterized by progressive functional impairment and reduced capacity to respond adaptively to environmental stimuli. The aging process, among other factors, determines the life span of an organism, whereas age-associated abnormalities account for the health status of a given individual. Aging is associated with increased susceptibility to a variety of chronic diseases, including type 2 diabetes mellitus, cancer, and neurological diseases. Lung pathologies are no exception, and the incidence and prevalence of chronic lung diseases has been found to increase considerably with age.

Aging has various faces, and most importantly, it has no purpose. Age-related pathologies are believed to result from the accumulation of molecular and cellular damage that cannot be repaired by aged cells due to limited performance of somatic maintenance and repair mechanisms. Two major hypotheses provide a conceptual framework for aging. According to the **antagonistic pleiotropy** hypothesis by Williams (Evolution, 1957), natural selection favors genes that are beneficial early in life for the cost that they may promote aging later in life. The **disposable soma** theory put forward by Kirkwood (Nature, 1977) proposes that the organism optimally allocates its metabolic resources, chiefly energy, to maximize reproduction, fitness, and survival. This comes at the cost of limited resources for somatic maintenance and repair causing accumulation of molecular and cellular damage. This concept supports the observation that the aging process is stochastic in nature and that there is individual plasticity.

The objectives of this book are to increase our awareness and knowledge of the physiological and accelerated mechanisms of the aging lungs given the expected increase in the aging population in the coming years. We would like to stimulate research on the molecular aspects of lung aging by combining chapters on the general hallmarks of aging with chapters on how to analyze lung aging by experimental approaches and chapters on the molecular and clinical knowledge on physiological and premature aging in lung disease.

As outlined in Chapter 1, the aging population will be more and more vulnerable to developing pathological conditions due to age-associated morbidities. Chapters 2–7 summarize characteristic cell-autonomous and systemic hallmarks of aging. While Chapter 2 gives an overview on the transcriptomic signatures of the aging organism, Chapters 3 and 4 introduce loss of proteostasis and the molecular details of telomere dysfunction, respectively. In Chapters 5 and 6, cellular senescence – the cell-autonomous aging program – is outlined in detail, and cellular signaling pathways that control senescence are elucidated. Chapter 7 provides an overview on the age-related changes of the immune system. Chapters 8–14 focus on the aging lung and age-related pathologies of the lung. Chapter 8 introduces the physiological aging process of the lung which is characterized by senile lung emphysema and the age-related decline in lung function in the elderly. Mouse models to explore the molecular nature of age-related lung pathologies are summarized in Chapter 9. Early damage of the immature lung as observed in neonates contributes to premature lung aging as outlined in Chapter 10. The aging lungs present featured changes of the extracellular matrix (Chapter 11) and of the mesenchymal stem cell compartment (Chapter 12). While age-related changes in tissue repair such as altered

matrix remodeling and stem cell recruitment add to fibrotic pulmonary diseases, telomere dysfunction and cellular senescence are hallmarks of premature aging in chronic obstructive pulmonary disease (Chapter 13). Immunosenescence and inflamm-aging both promote impaired host responses to respiratory infections in the elderly as outlined in Chapter 14.

We hope that this book will attract basic and clinical scientists to study the mechanisms of aging in general and of the lung in particular. We are confident that the book will contribute to our understanding of age-related lung diseases, and we wish you pleasure reading this book!

1 The Demography of Aging

David E. Bloom[1] and Sinead Shannon[2]

[1] *Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, USA*
[2] *Department of Health and Children, Dublin, Ireland*

1.1 Introduction

Throughout the world, people are living longer, healthier lives, and the proportion of older people is growing more rapidly than ever before, causing a dramatic shift in the global population age structure. These trends have been clear for several decades, and with each passing year, research reveals more about how the changing demographic structure is likely to affect individuals and societies. The ongoing changes will have implications for the development of policy in a number of areas – such as health, pensions, education, finance, and job structures – and although population aging is frequently presented as a threat, mitigating factors can dramatically alter its impact.

This chapter examines current age profiles throughout the different regions of the world. It starts with the factors contributing to the growth in the absolute numbers and proportion of older people and then looks at the factors contributing to the potential economic and health impact of aging. On the health front, the challenge will be to balance longer lives with an increase in the number of healthy years. If this can be done, it will help society control outlays on health and social care, along with enabling older people to live more productive, fulfilling lives.

1.2 Demographic trends

Let us start with the sequence of demographic changes known as the **demographic transition** – which all countries experience at varying paces and to varying degrees as they evolve from agrarian societies to modern industrial ones. This transition has four phases: (i) pretransition equilibrium at high levels of both mortality and fertility; (ii) mortality declines and fertility remains high, leading to a growth in the size of the population; (iii) population growth reaches its peak, followed by a decline in the crude birthrate that is faster than the decline in the crude death rate, leading to a slowing of population growth; and (iv) posttransition equilibrium at low levels of mortality and fertility [1].

Molecular Aspects of Aging: Understanding Lung Aging, First Edition. Edited by Mauricio Rojas, Silke Meiners and Claude Jourdan Le Saux.

In Europe and North America, the first phase took place during the several hundred years prior to the Industrial Revolution. It was typified by a high birthrate and a death rate that fluctuated because of epidemics and famines. After the Industrial Revolution, European countries started to see a decline in the mortality rate as public health improvements began to have an effect. In the two decades following World War II, the birthrate rose initially but then gradually declined throughout the remainder of the 20th century while the mortality rate also fell. The current stage of the developed world's demographic transition is characterized by a birthrate at replacement level (roughly 2.1) or below in many countries and a steady increase in longevity.

1.2.1 Fertility rates

In developed countries, fertility rates have been falling for a number of decades and reached replacement level around 1975 [2]. The European Union (EU) experienced a sharp fall in fertility rates between 1980 and the early 2000s, reaching 1.47 in 2003. However, since 2005, there has been an increase in almost all countries in the EU-27, resulting in an average of 1.59 in 2009 [3]. In the United States, the rate now stands at 2.1 children – the long-run replacement rate [2]. While the global fertility rate can vary dramatically, UN figures show that the number of countries with high fertility has gradually declined and is projected to continue falling. In 2000–2005, 56 countries (out of 192) had a total fertility of 4.0 or higher but by 2045–2050, the fertility rate, even among what are today's developing countries, is projected to fall to roughly 2.2 (and to about 2.8 in the least developed countries) [2].

1.2.2 Mortality rates and life expectancy

In the past, increases in life expectancy stemmed disproportionately from reductions in child mortality rates, but in the future, the UN predicts that the impetus will increasingly come from a reduction in mortality at the older ages.

Back in 1700, life expectancy at birth in England, which was at the time one of the richest countries in the world, was only 37 years [4]. The development of antibiotics and vaccines and subsequent improvements in hygiene, sanitation, and public health led to reductions in mortality at all ages, especially in childhood. More recently, as countries became more prosperous, economic development contributed to improved nutrition, immunization against common diseases, and a consequent reduction in death rates worldwide. It is thought that the introduction of clean water and improved sanitation in the United States during the late 19th and early 20th centuries may have been responsible for reducing mortality rates by about half and child mortality rates by nearly two-thirds in major cities. In the country overall, the death rate fell by 40% – an average decline of about 1% per year [5].

Globally, infant mortality has fallen from 51 deaths per 1000 in 2000 to 42 in 2010, with the rate projected to decline to 23 per 1000 by 2050 [2]. In OECD countries, infant mortality rates have seen a dramatic reduction from a level of 41 deaths per 1000 births in 1970 to an average of 8 deaths in 2010. However, substantial variations occur within countries. In the United States, for example, the infant mortality rate for children born to African-American mothers is more than double that for white women (12.9 vs. 5.6 in 2006) [6, 7].

Life expectancy at birth varies greatly across countries and levels of development, from as low as 57 years in less developed regions (2005–2010) to 77 years in more developed regions. Although, globally, it is predicted to increase to 69 years by 2050, this will depend

largely on succeeding in the fight against HIV/AIDS and other infectious diseases. In the EU-27, life expectancy for men in 2009 ranged from 67.5 years in Lithuania to 79.4 in Sweden [8].

1.2.3 Proportion of older people

The effect of increasing life expectancies and low levels of fertility, sustained for decades, has been an overall increase in the proportion of older people, accompanied by a lower proportion of younger people. In the United States, partly as a result of lower fertility, the population is growing slowly and beginning to age rapidly. For example, between 2010 and 2011, the number of young people (aged under 20) increased by only 375,000 (0.4%), while the number of people aged 60 and older (the 60+) increased by 1.58 million (2.8%) [2].

The UN estimates that, globally, the proportion over 60 will increase from 11% to 22% by 2050 (see Figure 1.1) – and will reach 28% by 2100. Although the world's population will triple in size by 2050 (from 1950), the number of people who are 60+ is expected to increase by a factor of 10, and those 80+ by a factor of 27 [2].

The proportion of people aged 60+ is not only changing over time but also varies greatly by region. Among countries, Japan currently has the largest proportion of people (30%) aged 60+ – a title that it is expected to still hold in 2050 when the figure reaches 44%. By then, every country in the world is expected to have a higher 60+ share, at which time one-third of the world's population will be living in countries with a higher proportion of older people than Japan has now [2]. Currently, the US share of 60+ is 18% (57 million), which is expected to rise to 27% (107 million) in 2050 – and to 31% (149 million) by 2100.

Similar trends appear in the population aged 80+, with Africa the only region not projected to have a very rapid increase in the proportion of the population in this age group. In the United States, the share of those aged 80+ is predicted to rise to 8% (32 million) by 2050, up

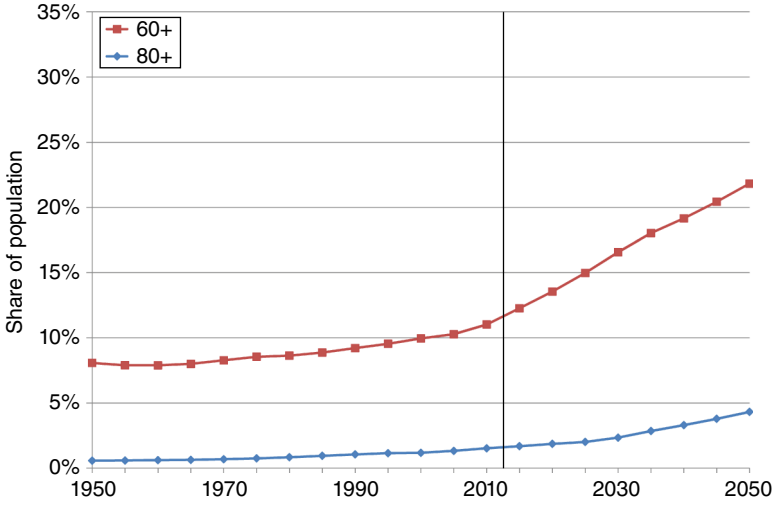

Figure 1.1 Increasing share of 60+ and 80+ population.

from 4% (12 million) in 2010. By 2050, the number of US centenarians is projected to reach nearly half a million [2]. The impact of all these demographic changes is that:

- The number of people aged 60+ will overtake the number of children (those aged 0–14) by 2047 [2].
- The bulk of population growth is expected to come from the developing world – with Africa's population projected to rise from 1 billion in 2010 to 3.6 billion in 2100.
- By 2100, only about 13% of the world's population will live in today's rich countries, down from 32% in 1950.

Of course, the rate of change in the share of older people in the population will vary from country to country, but less developed regions as a whole will experience a more rapid pace of growth. The countries that are expected to age most rapidly between 2010 and 2050 are primarily in the Middle East and Asia, while the least rapidly aging countries are in Africa [2].

1.3 Impact of aging

Over the past few decades, as population aging has become an issue for governments, particularly in the developed world, there has been considerable debate about whether we can expect the additional years of life to be healthy and active ones and whether governments will be able to meet the social and economic challenges that aging brings.

1.3.1 Noncommunicable disease trends

The prevalence of chronic conditions – known as noncommunicable diseases (NCDs) – has risen during the past two decades in both developed and developing countries [9]. Success in reducing communicable diseases has led to the dramatic increase in life expectancy (particularly in developed countries). However, the concern now is that the increase in the prevalence of NCDs will lead to a growth in the aggregate disease burden (because NCDs, by their nature, are generally long-lasting) and ultimately result in unsustainably high health costs (because they are typically expensive to treat). Moreover, any increased health costs may need to be paid by a relatively smaller working-age population because of the changing demographic structure.

The World Health Organization (WHO) estimates that in 2008, the four main NCDs (cardiovascular disease (CVD), cancer, chronic respiratory diseases, and diabetes) were responsible for the deaths of more than 31 million people worldwide – with about one-fourth of all NCD deaths premature (under 60 years) [9].

In the United States, it has been estimated that 65% of all health-care spending is on people with at least one chronic condition and that two-thirds of all Medicare spending is on people with five or more conditions [10]. This in itself is not necessarily a negative statement; rather, it is a reflection of the reduction in other causes of death such as communicable diseases and accidents. The prevalence of NCDs is rising in less developed regions, with roughly 80% of all NCD deaths now occurring in low- and middle-income countries [9]. Of note, NCD mortality appears to be more premature in low- and middle-income countries than in high-income countries. This presumably reflects the fact that in poorer countries risk factors are more prevalent and there is less prevention, early detection, and access to treatment.

Although deaths from heart disease, cancer, and stroke are declining, those from chronic obstructive pulmonary disease (COPD) are growing. Lung problems – such as COPD, chronic

bronchitis, emphysema, asthma, and airflow obstruction – are among the key contributors to the global burden of disease. COPD was the sixth leading cause of death worldwide in 1990 and is expected to become the third by 2020. According to WHO estimates, 235 million people currently have asthma [11] and 65 million people have COPD [12]. Among cancer deaths, lung cancer is the biggest killer throughout the world [9].

How prevalent is COPD in the United States? The figure varies between 3% and 10%, depending on the diagnostic criteria. The Centers for Disease Control and Prevention puts the figure at 6.3% of adults [13] and estimates that the disease is responsible for about 700,000 hospitalizations and more than 130,000 deaths in 2009. By 2020, it is expected to be responsible for the deaths of more individuals than stroke. Moreover, there is evidence that COPD may be underdiagnosed and undertreated in older people [14].

1.3.2 Risk factors

NCDs stem from a combination of modifiable and nonmodifiable risk factors. The latter refers to characteristics that cannot be changed by an individual (or the environment), such as age, sex, and genetic makeup. The former refers to characteristics that societies or individuals can change to improve health outcomes – primarily (i) poor diet, (ii) physical inactivity, (iii) tobacco use, and (iv) harmful alcohol use. The pathway from modifiable risk factors to NCDs often operates through what are known as **intermediate risk factors** – which include overweight/obesity, elevated blood glucose, high blood pressure, and high cholesterol [15]. Environmental toxins present in the air and water and on land also appear to play a role.

The WHO Global Status Report on NCDs (2010) found that the key underlying causes of death globally from NCDs are raised blood pressure (responsible for 13% of deaths), tobacco use (9%), raised blood glucose (6%), physical inactivity (6%), and overweight/obesity (5%) [9]. It also estimated that smoking causes about 71% of all lung cancer deaths and 42% of chronic respiratory disease [16]. The prevalence of these risk factors varies among regions and by gender and income level. In high-income countries physical inactivity among women, total fat consumption, and raised total cholesterol were the biggest risk factors, whereas in middle-income countries tobacco use among men and overweight and obesity were the biggest contributors to NCDs. The prevalence of smoking is higher in middle-income countries than in low- or high-income countries, and in all income groups, higher among men than women. Of the six WHO regions, the highest overall prevalence for smoking in 2008 was estimated to be the European region, at nearly 29% [9].

People in high-income countries are more than twice as likely to get insufficient exercise, with 41% of men and 48% of women insufficiently physically active, compared with 18% of men and 21% of women in low-income countries [9].

Obesity is more prevalent in high-income countries, where more than half of all adults are overweight and just over one-fifth are obese. However, overweight/obesity has recently started to affect lower-income countries, with the increase in prevalence from 1980 to 2008 (a doubling) greater than in upper-middle- and high-income countries [17].

In developing countries, the increase in NCDs can be attributed to factors less common in developed countries, such as malnutrition in the first 1000 days of life and environmental pollution – even though the major risk factors are also common in developing countries [18].

Within countries, the difference in life expectancy between the highest and lowest socioeconomic groups is also increasing, reflecting the greater prevalence of NCDs at younger ages in lower socioeconomic groups. In addition, mortality from NCDs shows a threefold difference between the highest and lowest occupational classes in some countries – perhaps

reflecting in part that those with lower education levels are less likely to receive a medical diagnosis, and even after diagnosis, experience greater difficulty in managing their conditions, or adhering to a disease management program. The evidence also suggests that it is education level rather than income level that has the greatest impact on health [19].

1.3.3 Impact of NCDs on health and disability

One of the key issues in relation to the rise in NCDs is whether they result in a burden, either for the individual or for the state. Living with an NCD for many years may not represent a major burden to the individual or his/her family unless the disease results in disability or infirmity and prevents them from continuing to work. However, lengthy periods of ill-health or disability will raise the cost of providing health services to the increasing numbers of older people. As all individuals must die from some cause, the aim must be to reduce the impact of the disease and minimize any reduction in health-related quality of life for the individual – and if possible, compress the period of illness or disability into a shorter period of time.

Research has not fully clarified how NCD trends are linked to the prevalence of disability and whether an extension of life expectancy will result in additional healthy years or an expansion of morbidity. Differing theories have been put forward since Gruenberg [20] predicted a pandemic of chronic diseases or expansion of morbidity. In 1980, James Fries [21] suggested that instead we would see a **compression of morbidity** – that is, the postponement of disease and disability and the compression of ill-health, activity limitation, or disability into a shorter period of time prior to death. In 1982, Manton [22] proposed a middle-ground theory that argued in favor of the emergence of a **dynamic equilibrium**, where the prevalence of disability would increase as mortality falls but the severity of disability would decline.

Who is right? The evidence supporting each of these theories is mixed, partly because of differing definitions of disability. As for the compression of morbidity thesis, some studies are supportive. For example, one of them that compared two groups of over 50s over a period of 21 years found that those who undertook regular vigorous exercise (members of a running club) reached a particular level of disability 12 years later than those in the control group (7 years vs. 19 years) [23]. However, others argue that there is substantial evidence to suggest that progress toward the elimination or delay of disease linked to aging has been limited – for example, the incidence of a first heart attack has remained relatively stable between the 1960s and 1990s, and the incidence of some of the most important cancers has been increasing until recently [24].

With regard to the dynamic equilibrium theory, one particularly supportive study argues that while the prevalence of many diseases has increased, there has been a reduction in the impact of such diseases on the individual, being both less lethal and less disabling [24]. Differing suggestions have been put forward to explain the variations and apparent contradictions between countries and over time. Deeg suggests that the initial level of disability may influence findings – that is, countries with initially high levels of disability provide more potential for reduction and therefore compression, while others with low starting levels (based on the time from which data is available) offer less potential for reduction [25]. However, Robine and Jagger [26] suggest that the demographic and epidemiologic theories of population health transition provide the answer. They argue that countries, genders, and socioeconomic groups within countries may be at different stages of a general health transition: first, people survive various illnesses

into older ages and disability rises; then, the health of older people improves through various means and the number of years lived with disability decreases; but finally, the number of years lived with disability rises again when the average age of death rises to the extent that many people spend their last years at advanced old age with multiple chronic diseases and frailty [24, 27].

1.3.4 Increase in multimorbidities

Many of the most common NCDs frequently occur with other conditions, and growing numbers of people have more than one condition, especially if they smoke. The presence and increasing prevalence of multiple and costly comorbidities, particularly in later life, suggests a clear need for a new approach to preventing and treating such conditions. Each condition can influence the care of the other conditions by limiting life expectancy and the ability to remain active. Multimorbidities can also lead to interactions between therapies, and often, the treatment of one condition can inhibit the treatment for or exacerbate another condition.

Risk factors such as tobacco smoking can increase the likelihood of a person having a number of chronic conditions simultaneously. Studies show that COPD, particularly among older people, is characterized by a high prevalence of comorbid conditions such as CVD, muscle wasting, and osteoporosis. Among patients with COPD, the prevalence of heart failure varies across studies between 7.2% and 20.9% (depending on the diagnostic criteria used in the research); among patients with heart failure, the number of people diagnosed with COPD varies from 10.0% to 39.0% [28]. Depression, anxiety, and malnutrition are also common among older COPD patients [29].

The fact that people with chronic illnesses may be treated for a number of conditions, often by different medical professionals, results in their being prescribed a number of different drugs at the same time. In some cases, these drugs may have adverse interactions. In Europe, up to one-third of people aged 65 years and older use five or more prescription medications [30]. Boyd et al. [31] showed how, by following existing clinical practice guidelines, a hypothetical 79-year-old woman with COPD, type 2 diabetes, osteoporosis, hypertension, and osteoarthritis would be prescribed 12 medications, a mixture that risks multiple adverse reactions among drugs and can lead to avoidable hospitalization. Indeed, this is a major concern—among older adults, up to 16% of hospital admissions are due to adverse drug reactions [32].

1.3.5 Impact on expenditure

There is growing concern that population aging will drive up health-care expenditures. This concern is consistent with the positive cross-country correlation observed between the rising share of gross domestic product (GDP) devoted to health-care expenditures and the rising share of population at the older ages. However, evidence from a number of countries suggests that the costs associated with intensive hospital use prior to death are lower at older ages.

In the United States, the difference between hospital costs for those who died aged 85 and older is estimated to be 50% lower than for those who died between 65 and 69 [33], while in Denmark these costs are estimated to be 70% lower [34]. Why is this so? A Canadian study that sought to explain these differences identified a drop in hospital costs by 30% to 35% between the oldest and youngest age groups but found that the number of days spent in the

hospital varied little between the two age cohorts. What was significant was the intensity of services received in the hospital day, a finding supported by research carried out on U.S. Medicare costs [33, 34]. Other research suggests that the bulk of expenditure for most people is likely to be required during the last year or two of life, regardless of age [37].

1.4 Policy responses

The prevalence of NCDs tends to be linked to either age or lifestyle – and fortunately, lifestyle-related causes can be modified, mitigated, or prevented by early intervention. In fact, World Bank evidence suggests that more than half of the NCD burden could be avoided through effective health promotion and disease prevention programs that tackle the prevalence of risk factors and reduce the number of premature deaths attributable to NCDs [38].

1.4.1 Preventing and managing NCDs

These interventions can occur at different stages in life: primary prevention could take place throughout the life course, focusing on the modifiable risk factors – such as better nutrition, more physical activity, higher rates of immunization, and health literacy (especially on smoking and alcohol risks). Secondary prevention can be most relevant to people aged 40–50 by focusing on known risk indicators (such as blood pressure, cholesterol, and low bone mass) – perhaps by giving users of health services more information and guidelines for self-management. Tertiary prevention occurs when the disease is present; it includes better disease management and rehabilitation from COPD, stroke, etc.

Many countries are developing new policy frameworks to prevent the occurrence of chronic disease and to manage the diseases in a way that delays the onset of complications and reduces emergency hospital admissions and use of expensive acute services. These policies include (i) increased health information, screening, and health checks for particular age groups, as well as deterrents such as increased taxation for tobacco or alcohol; (ii) less marketing of particular foods and beverages to children; (iii) taxes on foods that are high in sugar, salt, or fat; and (iv) earlier diagnosis and better treatment.

There is ample evidence of the success of such policies and that even simple measures can contribute to a reduction of the level of premature death. The WHO and the NCD Alliance (an association of "four international NGO federations representing the four main NCDs – cardiovascular disease, diabetes, cancer, and chronic respiratory disease") estimate that primary prevention measures can prevent 80% of premature heart disease, 80% of type 2 diabetes, and 40% of all cancers. Similarly, there is some evidence that secondary prevention can lower service use by between 7% and 17% at a very low cost [38]. Earlier and better treatment initiatives have reduced the number of people with heart disease and improved survival after cardiovascular events, which, in turn, has lowered CVD deaths [39].

A case study in North Karelia, Finland, exemplifies how the preventive approach can succeed. During the 1960s, the region had one of the highest rates of death in the world from coronary heart disease (CHD), especially among men. Following a large-scale preventive program, involving local and national authorities, the media, NGOs, supermarkets, the food industry, agriculture, health services, schools, and WHO experts, the level of smoking had fallen dramatically, dietary habits had improved, and most significantly, the prevalence of CHD had decreased [40].