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General introduction

1.1 Introduction

The world celebrated the new millennium with more than 6 billion people. Significant improvements in population health have occurred in the past half-century, markedly increasing the number of older people in industrialized countries. Together, the rapidly expanding older population in developing countries and the older population in the industrialized countries, form a global, aging force that is increasing the burden on the public health system and on medical and social services. More than 65 percent of Americans aged 65 years or older, for example, currently have some form of cardiovascular disease (Kane, 2002) and 30 percent of deaths are due to cardiovascular disease. The longer people survive and the older they become, the more health becomes a dominant issue. Along with an aging population come alarming health problems such as chronic disease (i.e. cardiovascular disease) and disability. The focus of this study is on chronic disease, specifically cardiovascular diseases, as they cause much human suffering, create substantial threats to economies of individual countries, and contribute to health inequalities between countries and within populations worldwide (WHO, 2002).

Uncertainty about the future health of the elderly population is known in the international context as the *compression* versus *expansion of morbidity*. The term morbidity refers to a manifestation of ill health. The compression of morbidity hypothesis assumes that the length of life is fixed and chronic disease and related disability can be postponed to older ages (Fries, 1980). The opposite hypothesis, i.e. that of the expansion of morbidity, states that mortality reductions will produce more years with morbidity and related disability (Gruenberg, 1977; Kramer, 1980; Verbrugge, 1984; Olshansky et al., 1991). Both hypotheses, that of the compression and that of the expansion of morbidity have been debated in relation to ageing over the past decades. The debate has focused either on degenerative diseases (Barendregt and Bonneux, 1998) or disability (Crimmins et al., 1994; Nusselder, 1998) of the older population. Little attention has hitherto been devoted to cardiovascular disease and its risk factors. Cardiovascular disease is the major chronic disease. Cardiovascular disease is the number one killer in the world and it contributes to disability, diminished quality of life, and greatly increases health care

costs. Its burden on society is increasing (WHO, 2002). The subject of this book is the development of a model within the framework of the compression of morbidity theory for cardiovascular disease, its subtypes in the life history of cardiovascular disease and its risk factors. In the greater debate on compression or expansion hypotheses, the compression or expansion of specifically cardiovascular morbidity and its risk factors is a new concept in public health research.

The compression of morbidity hypotheses is investigated in relation to the life history of cardiovascular disease and its risk factors, by means of consistent application of the time-honored multistate life table (MSLT) technique to the longest follow-up study in history- the prestigious 'Framingham Heart Study'. The methodology applied in this study can be described as a new public health approach to the compression of morbidity debate "*coupling demographic techniques and the framework of epidemiology*".

Section 1.2 of this introductory chapter offers an overview of the compression versus expansion of morbidity hypotheses, with a description of the changes occurring over time in mortality and morbidity. A general framework for integrating morbidity and mortality is described in Section 1.3. In Section 1.4, we describe the cardiovascular disease process and its risk factors. The research objectives are formulated in Section 1.5. The organisation of this book is summarised in Section 1.6.

1.2 The changes in mortality and morbidity

Mortality is a fundamental factor in population dynamics (Omran, 1971). The overall mortality rate of human beings has declined radically throughout the world during the last half centuries. Life expectancy at birth has doubled, infant and child mortality has declined significantly and mortality has shifted to older ages. The survival of the old-age population has increased substantially since 1950 (Vaupel et al., 1998). At present, in the low mortality countries, a longer life is often taken for granted. The global life expectancy at birth has increased from a global average of 46 years in 1950 to 66 years in 1998 (Sen and Bonita, 2000). The twentieth century has seen a dramatic increase in the life expectancy of residents in the United States. The life expectancy at birth increased from 49 years in 1901 (U.S. Census Bureau, 1996) to 77 in 2000 (World factbook, 2001).

This remarkable increase in life expectancy has been guided by substantial changes in the age-at-death and cause-of-death patterns (Nusselder, 1998). These shifts in age and cause specific deaths are illustrated in the *epidemiologic transition* theory (Omran, 1971), which is an extension of the mortality component of the *demographic transition* (Mackenbach, 1994). The theory of epidemiologic transition has developed from the application of epidemiology, demography, and other social and health sciences to population dynamics. The focus of the theory is on the complex

changes in patterns of health and diseases; their demographic, socioeconomic, and biologic determinants; and consequences for population groups (Omran, 1971).

There are two established groups of researchers investigating mortality and life expectancy- one group, known as the promoters of *the limited-life-span paradigm* and another group known as the promoters of *the mortality-reduction paradigm*. The first group concludes that average life expectancy will not increase beyond 85 years of age (Keyfitz, 1978; Fries, 1980; Olshansky, et al., 1990; Olshansky and Carnes, 1994; Wilmoth, 1998). The arguments for this are provided by the evolutionary theory of senescence (e.g. substantial reductions in mortality rates at advanced ages are constrained by biological barriers), well known to researchers in the field of bio-demography (Fries, 1983; Carnes and Olshansky, 1993; Olshansky and Carnes, 1994). The second group argues that the decline in mortality rates will persist and may even speed up, even at the most advanced ages (Vaupel and Gowan, 1986; Vaupel and Lundstrom, 1994; Manton, et al., 1991; Guralink et al., 1988; Schneider and Brody, 1983). Based on the enormous increase in life expectancy in the past, this group predicts further increases up to as high as 100 years or even more in the near future (Manton et al., 1991; Vaupel and Lundstrom, 1994). However, viewpoints differ as to whether there is a biological limit to life expectancy. Some researchers believe that biological limits exist, but that future advances in technology (e.g. biomedical research) may nevertheless boost life expectancy up to 100-125 years or even 150-200 years (Manton et al., 1991).

What was ignored in the debate was morbidity. Traditionally, improvement in population health status has been measured on the basis of the increase in life expectancy of that population. The reason is simple- data availability and simple estimation procedure. Nowadays, in the industrialized countries where improvements in life expectancy are mainly caused by mortality reductions from chronic disease in older ages, thought-provoking doubt exist as to whether longer life expectancy means a reduction in morbidity (Gruenberg, 1977; Kramer, 1980; Verbrugge, 1984; Olshansky et al., 1991). This doubt about the development of morbidity, in particular in relation to the elderly population, has led to the formulation of three hypotheses: the *expansion of morbidity*, *compression of morbidity* and *dynamic equilibrium*.

The expansion versus compression of morbidity debate originated with papers by Gruenberg (1977) and Kramer (1980). They pointed out that the present advances of medical technology allow us to save the frail and disabled from dying from complications, and therefore that mortality reduction will produce more years with morbidity and related disability. Their hypothesis is also called 'failure of success', and would further lead to a 'pandemic of mental disorders and associated chronic disease and disabilities'. They based their argument on the fact that if the incidence of chronic disease (e.g. cardiovascular disease) and disability remains constant, but survival improves, the stocks of frail patients will increase.

The antithesis of expansion is compression, as is espoused by Fries (Fries, 1980; Fries, 1983; Fries, 1989). The main proposition of Fries is that the length of life is fixed. He argues that there is a natural limit to the life span- the so-called 'natural death' at around age 85. The process of rectangularization is viewed as a signal that life expectancy is reaching the maximum life span, preventing this from any further significant increase. Since the genetic potential of the human species is limited, mortality will cease to decline and the maximum limit be reached. Fries' second proposition is that chronic disease can be postponed by adopting a healthy life style. It is assumed that if morbidity can in reality be compressed into fewer years toward the end of a hypothetical 'full life span,' the quantity of disability over the whole life span will be abridged (Vita et al., 1998). Slowing down the onset of chronic disease and disability, while assuming a fixed length of life, produces a decline in the number of years with morbidity. This is called as 'compression of morbidity'. The notion of the compression of morbidity hypothesis has implications for the health care policies and costs and for the quality of lives of a population.

While the compression of morbidity hypothesis relates longer life (though limited) with an improvement in the healthfulness of life, and the expansion of morbidity hypothesis associates a longer life span with a fixed incidence, a third, intermediate view, known as the *dynamic equilibrium* hypothesis has been formulated by Manton (Manton, 1982). Manton argues that an equilibrium exists between life expectancy and the health and functioning of the elderly population. This hypothesis states that for many chronic diseases improved survival will come about by slowing the rate of progression of the primary disease process, i.e. the number of years lived with morbidity will increase, but the years lived with severe morbidity and disability will be relatively constant.

Numerous studies have tried to find empirical evidence for the expansion or compression of morbidity (Mathers et al., 1994; Perenboom et al., 1993; Robine, 1994; Wilkins, et al., 1994; Nusselder, 1998; Barendregt and Bonneux, 1998). Usually they operationalised expansion or compression in the generic term 'disability'. Some findings point towards expansion, some towards compression, and some towards neither. Several methodological papers have pointed out that the most commonly employed method (e.g. Sullivan method), that is based on prevalence-based information (Colvez and Blanchet, 1983; Wilkins and Adams, 1983; Bebbington, 1988; Crimmins et al., 1989; Rogers et al., 1989; Mathers, 1991; Robine et al., 1995; 1998; Crimmins et al., 1997; Hayward and Heron, 1999) is extremely complex. Compression and expansion depend on the kind of disease and kind of the disease epidemiology. At the very least, a distinction should be made between fatal and non-fatal disease (Manton, 1982; Olshansky et al., 1990). However, to our knowledge there is no empirical evidence as to whether cardiovascular morbidity and its risk factors compress or expand cardiovascular morbidity. In this study, we propose to operationalise the concept of compression

in terms of the number of years lived with cardiovascular disease and cumulative incidence (absolute compression) in the presence or absence of risk factors using the multistate life table approach. Methodologically speaking, multistate life tables were felt to be a better choice for estimating compression or expansion than the prevalence-based Sullivan (Sullivan, 1971) type method (Rogers et al., 1989; Barendregt and Bonneux, 1998; WHO, 2000).

1.3 Integration of morbidity and mortality: a general framework

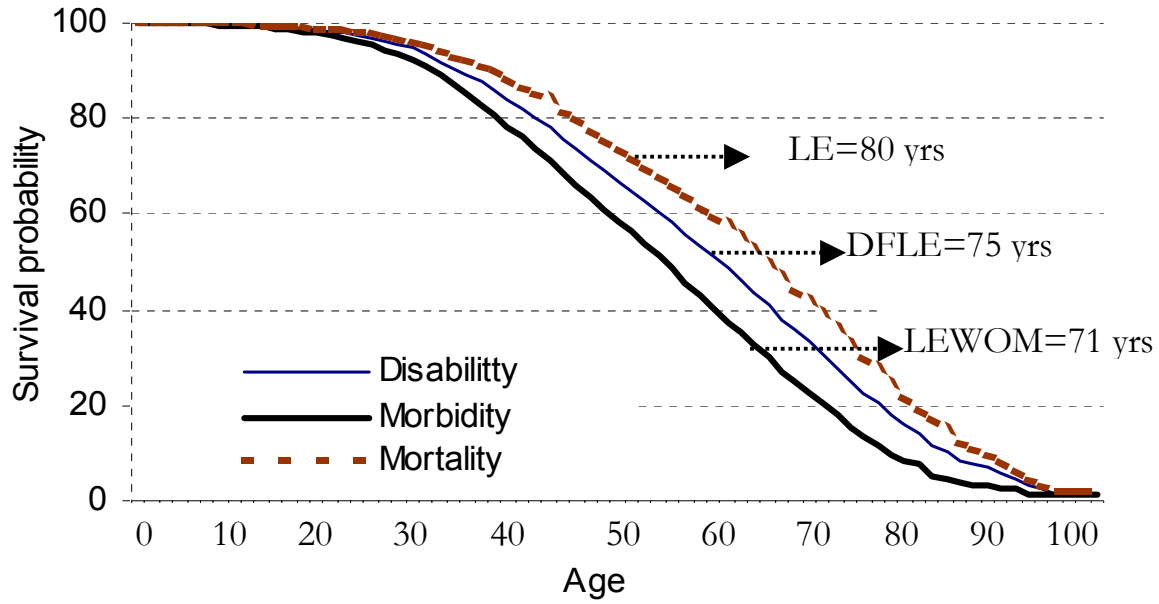
The main determinants of morbidity are the prevalence of a disease and the severity of that disease (Barendregt and Bonneux, 1998). The distinction between diseases or disorders, impairments, disabilities and the handicaps is the succession of events that may occur following disease. To describe the consequences of diseases, WHO (1980) introduced the concept of IDH- impairment, disability and handicap. Disease is defined as the abnormality that appears within individual (intrinsic situation). Impairments are "concerned with abnormalities of body structure and appearance and with organ or system function, resulting from any cause; in principle, impairments represent disturbances at the organ level". Disabilities reflect "the consequences of impairments in terms of functional performance and activity by the individual; disabilities thus represent disturbances at the level of the person". Handicaps are "concerned with the disadvantages experienced by the individual as a result of impairments and disabilities; handicaps thus reflect interaction with and adaptation to the individual's surroundings". However, in public health research, the health outcome of interest is the disability which a disease causes, or in other words disability is considered to be a dimension of disease. Thus chronic diseases such as cardiovascular disease bring disability into the life of the individual.

The general model of health transitions that allows a direct assessment of the health consequences of increasing survival was introduced by the World Health Organization (WHO) in 1984. This survival curve model provides a comprehensive framework and an analytical tool to integrate changes in mortality, morbidity and disability over the life course in a standard manner. It distinguishes between total survival, disability-free survival and survival without (chronic) morbidity (Figure 1.1). The survival curves used in the WHO models are determined by age-specific mortality, morbidity and disability and are calculated from the life table. In Figure 1.1, the area below the mortality curve represents total life expectancy (say, LE=80 years), the area under the disability curve represents disability-free life expectancy (say, DFLE=75 years) and the area under the morbidity curve is the life expectancy without morbidity (say, LEWOM=71 years). The difference between LE and DFLE measures life expectancy with a disability (LEWD: area between 'mortality'

and 'disability' curves). The area between the mortality and morbidity curve mirrors the expected duration of life with morbidity (LEWM). The sum of complementary life expectancies is equal to total life expectancy, for example, LEWOM plus LEWM is equal to total LE.

The general framework of the WHO health transition models enables us to assess whether or not changes in mortality and morbidity result in compression or expansion of morbidity. The survival and health status depends on the risk factor status, which is ignored in this model. For instance, people with an optimal risk in adulthood survive longer and remain in good health compared to the high-risk group. Therefore, the effect of risk factors on disease incidence and mortality and the balance in compression or expansion of morbidity can be analyzed using the same framework. For those with optimal risk the survival curves (Figure 1.1) will shift upwards and for those with high risk it will shift downwards. In this study, we have operationalised this framework, thereby incorporating single as well as multiple risk factors.

Figure 1.1 Mortality (hypothetical), morbidity (hypothetical) and disability (hypothetical) survival curves



The health status of a population is measured by combining morbidity and mortality. An indicator that summarizes the population health status over the life course and addresses the discussion of compression and expansion of morbidity is *health expectancy*. Health expectancy is defined as the average number of years an individual is expected to be healthy if current mortality and health status trends continue to apply (Mathers and Robine, 1994). Since health expectancy is in fact the combination of a life expectancy with a health concept, there are as many possible

health expectancies as health concepts (Robine et al., 2000). We can thus compute indicators such as life expectancy "in good perceived health" according to WHO definition of health, or "disease-free" life expectancy, "impairment-free" life expectancy, "disability-free" life expectancy and "handicap-free" life expectancy. The "dementia-free" life expectancy, proposed by Ritchie, is a good example of disease-free life expectancy (Ritchie, 1991). The "illness-free" life expectancy proposed by Newman (1988) is another example of combining morbidity and mortality data. In the field of mental health, general indicators of mental health expectancy have been produced as well (Gispert et al., 1998). Through the use of longitudinal data sets and new methodological techniques, researchers have started to compute active life expectancies – the expected duration in years of functional well-being according to the performance of activities of daily living (ADL) (Katz et al., 1983). This measure not only measures how long a sub-population can expect to live, but also what fractions of the expected remaining lifetimes will be spent in independent or dependent statuses (Rogers et al., 1989). We can compute life expectancy "without significant risk factor damage" (Manton, 1989) or more simply without "risk" (Rowe, 1990) to assess what we call "successful aging" (Rowe and Kahn, 1997). However, in this study the focus is mainly on life expectancy without cardiovascular disease, including its different manifestations, in presence or absence of potential risk factors.

1.4 Setting the scene

1.4.1 Cardiovascular disease

The subject of this study is to model the cardiovascular disease history and its risk factors. Cardiovascular disease is an established chronic disease for the population of developed and developing countries. Chronic diseases are illnesses that are prolonged, do not resolve spontaneously, and are rarely cured completely. Cardiovascular disease refers to variety of diseases and conditions affecting the heart and blood vessels. The major cardiovascular diseases are coronary heart disease (CHD), myocardial infarction (MI), stroke and congestive heart failure (CHF). Cardiovascular diseases are preventable. This disease causes a significant burden in mortality, morbidity, and health care cost.

Despite the gradual decline in cardiovascular death rates over the last few decades, these diseases are and will remain the number one cause of death in industrialized countries. In this region, 48.6 percent of deaths were caused by cardiovascular disease in the year 2000 (WHO, 2002). By 2020, 46.4 percent deaths are expected to be attributable to CVD in this region. Moreover, , CVD will soon become the main cause of death and disability in the developing world as well; by 2020, a third (33.8 percent) of all deaths are expected to be due to CVD (WHO,

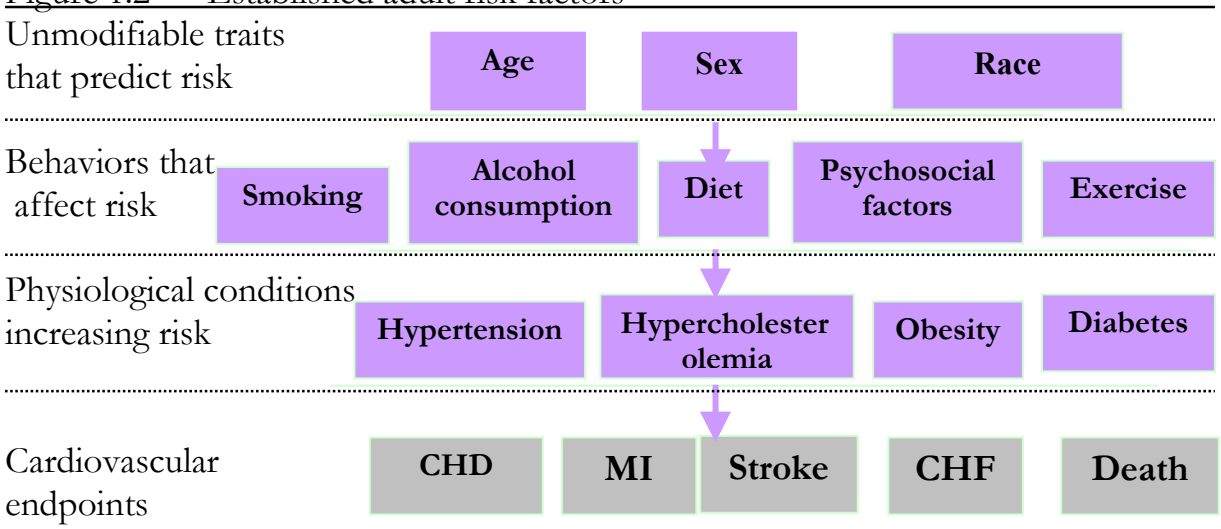
2002). In the year 2000, 16.7 million people died from CVD, accounting for 30.3 percent of all deaths worldwide; more than half of these deaths were in developing countries (WHO, 2001). Not only is cardiovascular disease a considerable health burden (e.g. high morbidity and high mortality), it causes also a significant health care cost (i.e. economic burden), which will continue to grow as the population ages.

The ongoing economic and technological developments taking place in the developing countries will in all likelihood cause the pattern seen in developed world to be repeated. The epidemic of cardiovascular disease is expected initially to emerge in those who are wealthy and subsequently to spread to those who are less wealthy. Likewise, when the epidemic starts to slow, this will first become apparent among the affluent, with the disease continuing to have a high prevalence in those who live in poverty. The burden of CVD, although already high in developed world, is therefore expected to increase on a global scale as the developing countries start to contribute significantly to this (WHO, 2002). The presence of rising CVD underscores the imperative need to develop effective and appropriate prevention policies.

1.4.2 Cardiovascular disease risk factors

A *risk factor* is a condition that elevates or raises our chances of getting a disease. Two types of risk factors of cardiovascular disease might be distinguished - adult risk factors and risk factors in early life. These early and later risk factors may well interact with each other. The adult risk factors and their impact on cardiovascular morbidity and mortality are the focus of this study.

Figure 1.2 Established adult risk factors

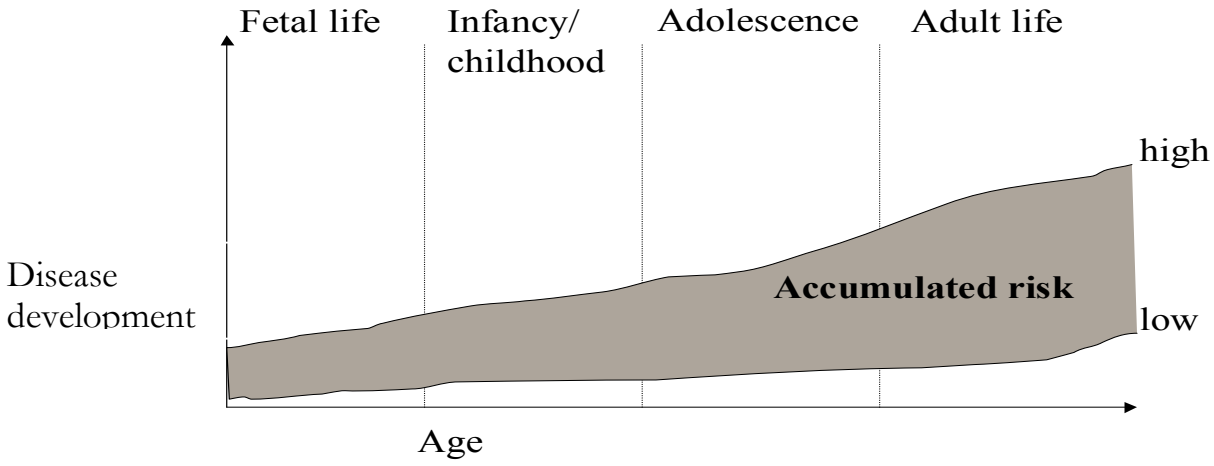


Source: Stolley and Lasky, (1995)

Most of the established adult risk factors for cardiovascular disease are shown in Figure 1.2. Some risk factors are modifiable and some are not. Age, sex and race are unmodifiable risk factors. The major behavioral risk factors are smoking, alcohol consumption, diet, psychosocial factors and physical exercise. Some of the physiological conditions such as hypertension, high cholesterol, obesity and diabetes are most important risk factors for cardiovascular disease.

The risk of cardiovascular diseases accumulates with age and is influenced by factors acting at all stages of the life span (WHO, 2002; Ben-Shlomo and Kuh, 2002). This life course epidemiology is new but growing. From this perspective, for instance, the development of cardiovascular disease starts during fetal development and is influenced by factors acting at different stages- infancy and childhood, adolescence and adult life (Figure 1.3). To explain the possible ways in which factors over the life course may act to cause chronic disease, so far only a few theoretical models have been advanced (Ben-Shlomo and Kuh, 1999; 2002). However, the most firmly established associations between cardiovascular disease and factors in life span are those between disease and the major known adult risk factors: tobacco use, obesity, physical inactivity, cholesterol, high blood pressure, and alcohol (Godlee, 1999; Elisaf, 2001). This study focuses solely on these adult risk factors.

Figure 1.3 Development of cardiovascular disease



Source: WHO (2002)

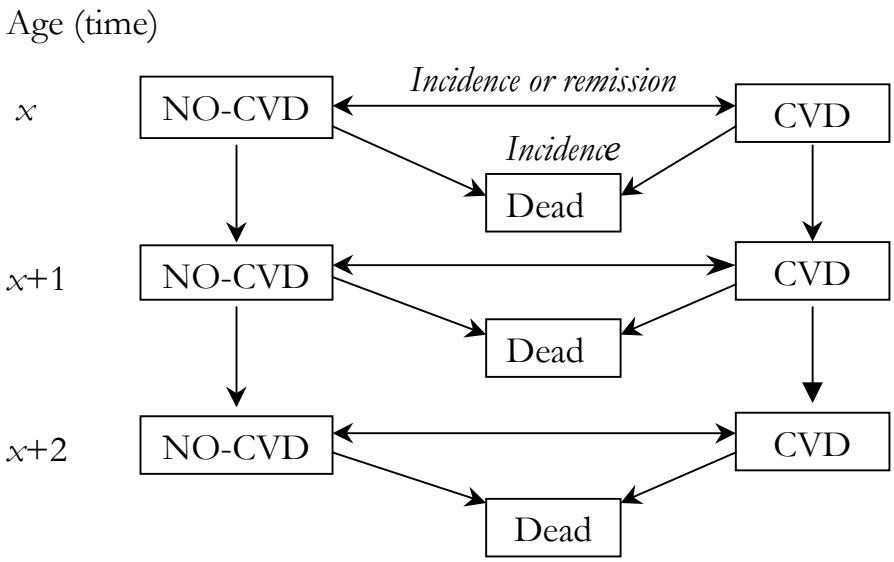
1.4.3 Basic model of cardiovascular disease

To estimate cardiovascular compression of morbidity and its risk factors we use multistate life table techniques. Multistate life table techniques have been used before to obtain consistent sets of data for chronic disease modeling (Hoogenveen et al., 2000). In public health, MSLT methodology has also been used to estimate

the population health status and to address the question of compression or expansion of morbidity (Crimmins et al., 1994; Nusselder, 1998; Nusselder et al., 2000; Barendregt and Bonneux, 1998). The main feature of this model is that it considers both the increment (inflow) and decrement (outflow) according to various diseases states of the population.

The basic model structure of cardiovascular disease is presented in Figure 1.4. There are three states in this model: NO-CVD (i.e. free of CVD), CVD and dead. At age x an individual could be in NO-CVD state or in CVD state. At age x+1 that individual can make transition to another state (either incidence or remission) or remain in that state. Life tables are usually presented in one-year age intervals, beginning with an arbitrary value at age x.

Figure 1.4 Basic (multistate life table) model structure of cardiovascular disease



We use the first 50 years of follow-up of the Framingham Heart Study (FHS) to construct multistate life tables. The *transition probability*, which is the basic parameter of the MSLT is estimated based on the *occurrence-exposure rate,* which represents the standard method. The occurrence-exposure rates are estimated directly from the data set. Estimation of the MSLT using occurrence-exposure rates has several advantages. *First*, the MSLT can be viewed from a life history perspective, allowing the reconstruction of the individual biography. *Second*, it provides us with a tool to analyze the changes in morbidity, disability and mortality rates within the framework of a single integrated model of population health and to summarize the information on changes in morbidity, disability and mortality into an integrated indicator of population health (Nusselder, 1998). Health expectancy is one of the best-known examples. *Third*, the observed occurrence-exposure rates enable the use of data in the presence of any type of censoring- left, right, double or

interval. *Fourth*, an MSLT can work as a tool to operationalize the conceptual model (Figure 1.1) to describe and visualize the association between changes in morbidity, disability and mortality and overall population health. *Fifth*, multiple covariates can be included in the construction of the MSLT. This means that we can combine MSLT with multivariate regression models. *Sixth*, this model can be used to clarify the debate of compression or expansion of morbidity hypotheses more accurately compared to the prevalence-based method.

We chose to consider the original cohort of the Framingham Heart Study to perform this study, because of the long-term follow up and accurate record keeping of the cardiovascular disease occurrences and deaths. The more impressive information is the 48 years consistent follow-up of the cardiovascular disease risk factors. This study offers a unique opportunity to assess the life history of cardiovascular disease and its risk factors. The FHS, combined with the robust multistate life table method offers an excellent means to pursue our object.

1.5 Research objectives

The objectives of this study are both methodological and substantive. We have two aims, namely to:

- *Explore the utility of the multistate life table for public health, specifically, to operationalise the debate on compression or expansion of morbidity.*

- *Model the cardiovascular disease life history and its risk factors and to investigate whether the risk factors of cardiovascular disease and its sub-types lead to expansion or compression of cardiovascular morbidity.*

To date, the question whether or not changes in population risk factors such as high cholesterol and smoking would lead to increased or decreased cardiovascular morbidity within the population has received little to no attention in the literature. The question of whether changes in population risk factor status leads to compression or expansion of cardiovascular morbidity is addressed using the first 48-years of follow-up of the original Framingham Heart Study cohort. We compare the cardiovascular life course between the optimal risk (e.g. normal body mass index) and high-risk category (e.g. obesity). We investigate whether cardiovascular risk factors (both single and multiple risk factors) at middle age compresses cardiovascular morbidity.

The compression versus expansion debate has grown more complex over the past decades. For instance, two recent studies reported that a population of non-smokers would experience more years lived with disability (Ferrucci et al., 1999; Martel et al., 2000), and one study reported that non-smoking compresses

morbidity both in absolute and relative terms (Bronnum-Hansen and Juel, 2001). In addition to furthering this complex debate, the present study, using the original Framingham Heart Study cohort allows us to measure the compression or expansion of disease-specific life expectancy, such as the life years lived with cardiovascular disease and life years lived free of cardiovascular disease in the presence or absence of risk factors.

We make an explicit distinction between prevalence-based and incidence-based measures. We explore the theoretical and practical aspects of the multistate life table approach and indicate the methodological innovation and utility of this method in public health research. In this study, the basic parameter for constructing the multistate life table is the occurrence-exposure rate. A method for calculating the occurrence-exposure rates using micro data is illustrated. We generalize the multistate life table, describing this in multiple covariate contexts i.e. bridging the multivariate regression models and multistate life table techniques. We illustrate the bootstrapping technique used to estimate the confidence intervals of the multistate life table outcomes.

Together with disease history, risk factor status in an important aspect in better understanding the complexity of the compression or expansion of morbidity issue. To better address the issue of compression of morbidity hypotheses, longitudinal data are needed. A recurrent problem with longitudinal data is that of missing values. We propose potential methods to impute missing values of the risk factors in a repeated measurement study. We selected smoking as an example of a risk factor career. The life history of smokers and nonsmokers is demonstrated by constructing a multistate smoking status life table.

To construct a life table (with or without covariates), we need age-specific transition rates. Transition rates can be derived directly from the data set (e.g. occurrence-exposure rates) or can be estimated by fitting regression models to the data. Two well-known models developed by Cox and Gompertz are considered and assessed with the aid of empirical rates and life table outcomes.

This study compares the burden of cardiovascular disease in terms of lifetime risk and life years lived with disease between long time smokers and non-smokers. We address the question of whether non-smoking shortens the number of years lived with cardiovascular disease, i.e. leads to compression, given the competing forces of an increased risk of cardiovascular disease and increased mortality in smokers.

We focus on the risk factor status at middle age (age 30 to 50) and its impact in the older ages of life. One of our objectives is to investigate the association of the risk factor status at middle age and the incidence of cardiovascular disease and its subtypes, and post-disease mortality over a long-follow-up. Whether changes in population risk factors such as high cholesterol and smoking lead to increased or decreased cardiovascular morbidity within the population has previously not been

examined in the literature. This question is addressed in the present study by integrating multistate life table and the multivariate regression models. Performing both univariate (i.e. single risk factor) and multivariate (multiple risk factors) analysis allows us to investigate whether risk factor status at middle age compresses cardiovascular morbidity.

1.6 Outline of this book

This book is structured into ten chapters, of which *Chapter 1* is the general introduction. In *Chapter 2*, we review the multistate life table technique and emphasize the potential utility of this method in public health research. The multistate life table is the basic tool that used throughout this study to measure the cardiovascular disease history and address the question of compression or expansion of morbidity. We explicitly differentiate between the prevalence and incidence measure of population health status. A concise overview of the mathematical construction of a multistate life table is given in this part of the study. We describe the equations, thereby focusing on micro data instead of macro data. We generalize the multistate life table by describing it in multiple covariate contexts. The input data and the possible output from the multistate life table are also illustrated. We demonstrate the possible methods to calculate the confidence intervals around the multistate life table measures. The fundamental difference between the multistate life table approach and the Sullivan method is described as well. Overall, this provides an overview of the theoretical and practical aspects of the multistate life table method and indicates the methodological innovation and utility of this method for public health research.

Chapter 3 demonstrates a method to produce occurrence-exposure rates using micro data. The construction of the multistate life table is illustrated step-by-step. Here, we transfer the well-described epidemiological measures into time based public health policy measures, such as the life time probability of cardiovascular disease, life years lived with cardiovascular disease and life expectancy free of cardiovascular disease. The indicators derived in this chapter of the study are integral to appropriate health planning and assessment of the potential population health value of various treatment and prevention strategies.

In *Chapter 4*, we propose potential methods for imputing missing values of risk factors in repeated measurement studies. In a longitudinal or panel study, missing data is very common. To construct the risk career (e.g. smoking career) , the imputation of such missing values is essential. Without imputation, we may not be able to capture the event that we would like to relate with the risk factor status at a nearby point in time. We consider two risk factors- smoking status and systolic blood pressure. Smoking status is selected to illustrate the imputation method for

categorical risk factors. The systolic blood pressure is selected to exhibit the imputation method for continuous risk factors.

Chapter 5 illustrates how a risk career can be reconstructed. We have taken a novel approach to analyze the "career or pattern over time" of risk factors, starting with a very common risk factor smoking. Multistate life tables are developed to capture different episodes of smoking. The described approach is a novel one, in that it demonstrates the importance of explicitly taking into account the changes in risk factors throughout life.

In *Chapter 6*, we compare the burden of cardiovascular disease in terms of lifetime risk and life years lived with disease between smokers and non-smokers. The basic question answered in this chapter is whether smoking compresses cardiovascular disease morbidity. We constructed multi-state life tables describing transitions through various cardiovascular diseases for smokers and non-smokers observed during 20 biannual observations in the Framingham Heart Study. To estimate the confidence interval of the multistate life table outcomes we use bootstrapping technique.

Chapter 7 provides as assessment of the well-known and widely used transition rate models of Cox and Gompertz. We compare the age-specific transition rates and the life table outcomes to know how the Gompertz and Cox models fit the empirical results, in presence or absence of covariates.

In *Chapter 8*, we perform both the univariate and multivariate regression analysis of the cardiovascular risk factors to investigate the association of the risk factor status at middle age (during age 30 to 50), the incidence of cardiovascular disease and its subtypes, and post-disease mortality over a long follow-up. We estimate, in long follow-up, how the effect of an adult risk factor is changed if one adjust this effect for the confounding influence of other factors.

In *Chapter 9*, we examine whether cardiovascular risk factor status compresses cardiovascular disease morbidity. We focus on the important CVD risk factors at middle age and their impact on CVD and mortality at later ages of life. We compare mainly the optimal and high risk. Initially, we explore the compression of morbidity hypotheses for each single risk factor status separately. Finally, the combination of several risk factors (i.e. multifactoral effect) and the compression of cardiovascular morbidity are investigated. In the multivariate case, the optimal risk profile is defined as a non-smoking individual, on average with optimal blood pressure (BP<120), optimal cholesterol level (SCL<200) and optimal BMI (BMI<25) between the ages of 30 and 50. If an individual is smoker, has high blood pressure (BP>140), high cholesterol (SCL>240) and obese (BMI>30) is considered to belong to the high-risk group. Empirical evidence is presented on the basis of which the impact of risk factors on cardiovascular life course can be assessed.

Chapter 10, the final chapter, summarizes the major findings and presents the implications of the findings. We synthesize the utility of this research in chronic diseases modeling. The chapter concludes with suggestions for future research on the life history of cardiovascular disease, its risk factors and compression of morbidity.

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