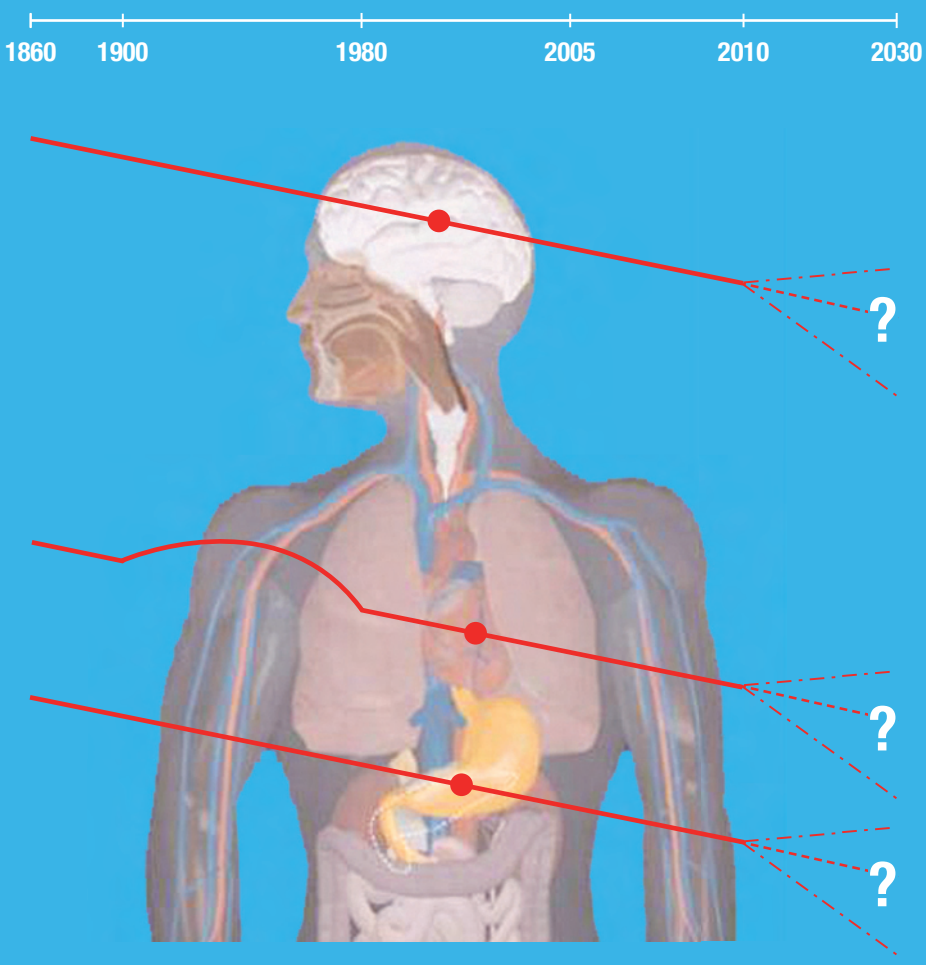
Trends in Mortality from Ischemic Heart Disease, Stroke and Stomach Cancer:

From Past to Future



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Trends in Mortality from Ischemic Heart Disease, Stroke, and Stomach Cancer: from past to future

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Proefschrift

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Copromotor:	Dr. A.E. Kunst

The true philosophy is to learn again to see the world
(Merleau Ponty)

To: **My family**
Mehrnoush
Arman and Armin

Contents

The following manuscripts are part of this thesis and have been published or submitted for publication:

Chapter 2

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *The relation of trends in IHD and stroke mortality with infant mortality rate. A time series study among cohorts born between 1860 and 1939 in seven European countries.* European Journal of Heart Failure Supplements. 2004; 3(1): 137.

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *Cohort-specific trends in stroke mortality in seven European countries were related to infant mortality rates.* J Clin Epidemiol**.** 2006 Dec; 59(12): 1295-302.

Chapter 3

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *Trends in stomach cancer mortality in relation to living conditions in childhood. A study of trends among birth cohorts born between 1860 and 1939 in seven European countries.* Eur J Cancer**.** 2006 Dec; 42(18): 3212-3218.

Chapter 4

Amiri M, Kunst AE and Janssen F. *The decline in ischemic heart disease mortality in seven European countries: exploration of future trends* (Submitted).

Chapter 5

Kunst AE, **Amiri M,** Bonsel GJ and Janssen F. *The decline in stroke mortality. Exploration of future trends in seven Western European countries* (Submitted).

Chapter 6

Amiri M, Kunst AE and Janssen F. *The decline in stomach cancer mortality: exploration for the future in Europe* (Submitted).

1

General Introduction

General introduction

1.1.Background

The common occurrence of chronic diseases – such as ischemic heart diseases (IHD) [1, 2], stroke [1, 2], and stomach cancer [1, 2]- in most populations and the attendant mortality, loss of independence, impaired quality of life, and social and economic costs are compelling reasons for public health concern. Although mortality from IHD [3], stroke [4], and stomach cancer [5] have fallen substantially in western Europe over recent decades, IHD and stroke remain among the leading causes of death in Europe [6-9]. Furthermore, elderly people constitute a growing part of the population [10] and therefore, the absolute number of deaths might continue to increase due to ageing of European population [11]. Together, IHD, stroke and stomach cancer, have figured prominently in the large shifts among causes of death, especially in industrial societies, during the 20th century. During this period, the mortality and morbidity rates of these diseases has changed rapidly in many countries, as a result of both increasing proportions of these populations attaining older ages and concurrent social changes. The epidemiology and prevention of these diseases involve the understanding of their causes, identification of means of prevention, and monitoring of populations to assess the changing burden of these diseases and measurable impact of interventions to control them. This thesis monitors seven European populations – i.e., Denmark, England and Wales, Finland, France, the Netherlands, Norway and Sweden. It assesses the changing impact of the above mentioned diseases over time by extrapolation of observed trends in the past. It projects the future profile of these diseases in seven European countries.

Cardiovascular diseases, of greatest public health concern for any country are those of the highest frequency now or potentially in the decades ahead. Wide geographic variations in rates and trends of mortality from IHD and stroke have been shown since the early 1950s [12, 13] and for incidence and case fatality from IHD by the WHO MONICA Project in the mid-1980s [14]. Particular conditions among the cardiovascular diseases, such as IHD and stroke, are important both as common causes of death and as causes of illness and disability among those who live with the disease and survive acute events. The epidemiologic research of past several decades has advanced understanding of major cardiovascular diseases to the point where their prevention is largely within reach, despite the increased knowledge on the cascade which leads to cardiovascular morbidity and death.

The picture for cancer is less consistent. As with IHD and stroke, cancer also represents a major cause of death and disability - with a changing (geographically) pattern [1, 2, 15]– mainly because of four potential explanations. Firstly, its etiology as a heterogeneous disease; some cancers which their exogenous factors apparently play dominant role, show changes according to the exposure involved; for example, cancers which are related to tobacco. Secondly,

ageing of the population; some cancers which apparently are associated with higher age have been introduced in recent years. Thirdly, population screening for some cancers; these screening programs have had some influences on incidence (increasing) and mortality (increasing or decreasing) of cancers. Finally, treatment improvements; treatment radically has changed prospects, on survival and morbidity, for some cancers such as hematological malignancies. Despite the successes in declining of malignancies' mortality, the background of most cancers is still only partially understood, at least insufficiently to guide prevention or therapy, and to make educated rather than statistical guesses about the future.

Taken together, we selected these three major diseases because of the role of IHD and stroke as first and second leading causes of deaths [1, 16-18], in spite of their declining trends in mortality in recent years [19-23]; and the etiology and possible relation of stomach cancer with early life conditions and therefore potential cohort effects. In addition, as stomach cancer had only few adult risk factors in common with the other selected diseases, its study promised new insights into the effects of early life conditions [16].

In addition, it is of limited interest to study the development of these diseases only in one country of region. It is obvious that results are more reliable and more likely to be generalizable, if more countries would be taken into account. Seven European countries –i.e., Denmark, England and Wales, Finland, France, the Netherlands, Norway and Sweden - have been selected. They seem suitable countries because they are heterogeneous enough, yet have a comparable level of wealth and socio-economic structure, and also their long-term mortality and population data come from data sources that are known to be of good quality [24-26].

This thesis monitors these seven European populations and assesses their changing burden of three diseases over time, and by extrapolation of results of observed trends in the past, project the future level of mortality from these diseases in seven European countries. Taken together, we expect these seven countries to allow for making inferences about future mortality from IHD/stroke/stomach cancer in countries with a similar profile.

We aimed to study changes and trends of the above diseases, related to determinants. Besides the obvious factors age and gender, we were interested in environmental background as this is a likely source for the rapid changes observed. Previous studies have suggested that early life factors may be important determinants of the trends and geographical differences in mortality from diseases in adults [27]. While such circumstances can not easily be measured, and, naturally, are unavailable for data in the remote past, it is generally accepted that proxies can be used for that purpose. Infant mortality rate (IMR) and gross domestic product (GDP) were selected because of practical reasons (availability of reliable data for a long-term in the past), and representativeness of these indices for health and economic situation of population in early life, respectively.

Studies have shown a strong geographical correlation between mortality from various causes of death in adulthood and infant mortality around the time of birth [28], where IMR was taken to reflect the living conditions in early life [29]. However, there is controversy about the association between early life conditions and mortality trends from these diseases. While several studies have shown the risk of IHD to be associated with adverse living conditions in early life [30-32], this finding has not consistently be replicated [33, 34] . Similarly, for stroke, some studies have observed a relation with living conditions in early life [31, 35], whereas others have not [9, 36]. Finally, although the importance of "environment" in early life in determining the risk for stomach cancer have been confirmed [9, 36]; however, the role of living conditions on mortality trends is not yet fully understood [37].

Some studies assessed the effect of living conditions in early life on time trends (instead of geographical differences) on adult mortality [38, 39]. These studies focused on the question of whether time trends in adult mortality reflect cohort effects or period effects. Cohort effects in turn would be suggestive of effects located in early life. Consequently, a useful contribution to these studies would be to assess cohort-specific trends in mortality in relationship to the IMR/GDP level at the time of birth of different cohorts. Such an analysis could contribute to a better understanding of mortality trend changes and the potential effect of early life conditions on these changes over time.

1.2.The objectives of thesis

The first objective is to describe the past trends in mortality from IHD, stroke, and stomach cancer in seven European low-mortality countries from 1950 to 1999 and to assess the explanatory role of early life factors. The second objective is to estimate the future mortality trends to 2030, based on extrapolation of the observed mortality trends in 1980-2005, in seven European countries.

1.3.Research Questions

The main research questions addressed in thesis are:

1. How did mortality from IHD/stroke/stomach cancer develop over the period 1950 to 1999 across Europe?

2. How was the relation between IMR and GDP (as proxies for early life conditions) and mortality from IHD/stroke/stomach cancer from 1950 to 1999 across Europe?

3. What will be the impact of mortality from IHD/stroke/stomach cancer in 2030, if the mortality trends of these diseases from 1980 to 2005 across Europe were to continue in the future?

1.4.Data and methods

1.4.1. Data:

To address the first research question of the thesis data on IHD, stroke, and stomach cancer mortality and population at risk, by year of death (1950-1999), sex, and five-year age group for these seven countries were obtained from national statistical offices and related institutes [40]; IMR data for the period 1860-1969 came from Mitchell for most countries [41], and from Turpeinen for Finland [42]. Historical national accounts data were used to estimate past national levels in gross domestic product (GDP) [43-45]. To bridge different ICD revisions, a general concordance table were used, in which the different codes for IHD, stroke and stomach cancer in the successive ICD revisions were linked [40].

For the second and third research questions, data for Denmark, Finland, France metropolitan, the Netherlands, Norway, Sweden and the United Kingdom on the number of deaths from IHD, stroke, and stomach cancer, and corresponding numbers of population at risk, by sex and five-year age groups for the years 1980 to 2005 have been obtained from national data sources (1980-1999) [46], and Eurostat (from 2000 to 2005). In addition, all-cause mortality rates were obtained from the Human Mortality Database (HMD). The future population numbers have been obtained from Eurostat (baseline variant) Furthermore, the fact that the International Classification of Diseases (ICD-6 to ICD-10) had been revised five times during this period has also been considered.

1.4.2. Methods

In both parts of this thesis, sex-specific age-standardized mortality rates, using direct standardization with a European standard population, were used to describe mortality trends. Pearson correlation coefficients were frequently used to quantify associations. The time periods were 1950 to 1999 (and birth cohorts of 1860 to 1939) for historic research for the **research questions 1 and 2**, and 1980 to 2005 for estimating the baseline trends for the projections for question 3.

For the historic analysis, we used **age-period-cohort (APC)** log-linear regression analysis (Poisson regression) to explore the trends of the past. For the future projection we used **age-period (AP)** log-linear regression analysis (Poisson regression) to estimate annual mortality changes (%). This method takes age differences into account. Furthermore, the impact of future mortality trends on life expectancy is assessed by means of the potential gained in life expectancy (PGLE), using cause-elimination life tables.

In this thesis, we refrained from using more complex models such as models that include data on disease occurrence and risk factors [47]. These models have as an advantage that patients are assigned to specific disease state which in turn allows estimating of health state specific life tables. Such a method ultimately provides more detail. However, these models also demand much more detailed data on disease progression, and age-sex specific rates of transitions between health states. Precision is thus obtained at the price of higher data demands, more assumptions, artificial staging of the disease, and difficulty in accounting for period effects. In contrast, regression models of mortality trends have the advantages of lesser data requirement and the possibility to use long term historical datasets [48]. Considering these advantages, we chose regression models, which were also recommended by Wilmoth [49] and European Association for Population Studies [50].

1.5.Structure of the thesis

The **first part** of this thesis; i.e., **Chapters 2** and **3**, aims to answer the **first two research questions** by dealing with the description of the past mortality trends in IHD, stroke, and stomach cancer in seven European countries. In these chapters, the role of period and cohort effects in the observed trends in the cohorts born from 1860 to 1939 was identified. **Chapter 2** describes the trends of mortality from IHD and stroke in relation to infant mortality rate (IMR). In **Chapter 3**, we analyzed the secular trends of mortality from stomach cancer. In both **Chapters 2** and **3**, we discuss the role of early life conditions and environmental factors (measured with IMR and GDP at birth) in mortality from IHD, stroke and stomach cancer from 1950 to 1999.

The **second part** of the thesis; i.e., **Chapters 4 to 6**, aims to answer the **third research question** on the future trends of mortality from the above mentioned diseases, by projecting the mortality trends towards 2030, based on the observed mortality trends in the time period of 1980 to 2005 in seven European countries. The projected mortality rates, absolute numbers of death, potential gained in life expectancy (PGLE) are compared to the related figures in 2005, in order to have an insight about the possible burden of mortality in the future. **Chapter 4** illustrates the probable declines in IHD mortality in seven European countries. In **Chapter 5**, we extrapolate the future trend of mortality from stroke in six European countries. In **Chapter 6**, we explore the trend of mortality from stomach cancer in 2030.

Chapter 7 focuses on the main discussion and elaborates on the determinants of the mortality decline in the past and possible projections in the coming years. Finally, **Chapter 8** provides a summary to the thesis in English, Dutch and Persian (Farsi).

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Part I :

The past mortality trends

2

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *The relation of trends in IHD and stroke mortality with infant mortality rate. A time series study among cohorts born between 1860 and 1939 in seven European countries.* European Journal of Heart Failure Supplements. 2004; 3(1): 137.

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *Cohort-specific trends in stroke mortality in seven European countries were related to infant mortality rates.* J Clin Epidemiol**.** 2006 Dec; 59(12): 1295-302.

Cohort-specific trends in stroke mortality in seven European countries were related to infant mortality rates

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Abstract

Objective: To assess, in a population-based study, whether secular trends in cardiovascular disease mortality in seven European countries were correlated with past trends in infant mortality rate (IMR) in these countries.

Study Design and Setting: Data on ischemic heart disease (IHD) and stroke mortality in 1950-1999 in the Netherlands, England and Wales, France and four Nordic countries were analyzed. We used Poisson regression to describe trends in mortality according to birth cohort, for the cohorts born between 1860 and 1939. Pearson correlation coefficients were calculated to determine associations between IMR and IHD or stroke mortality.

Results: IHD mortality increased for successive cohorts up to 1900, and then started to decline. Stroke mortality levels were virtually stable among birth cohorts up to 1880, but declined rapidly among later cohorts. A strong positive association was found between cohort-specific IMR levels and stroke mortality rates. There were no strong cohort-wise associations between IMR and IHD mortality.

Conclusion: These results support other studies in suggesting that living conditions in early childhood may influence population levels of stroke mortality. Future studies should determine the contribution of specific early life factors to the mortality decline in IHD and especially stroke.

Key Words: Europe, Mortality Trends, Ischemic heart disease, Stroke, Cohort Analysis, Infant mortality rate

Running title: Cohort-specific trends in stroke and IHD mortality in seven European countries

2.1. Introduction

While several studies have shown that the risk of ischemic heart disease is associated with adverse living conditions in early life[16, 17, 32-34], this finding has not always been able to be consistently replicated [35, 36] . For stroke, some studies have observed a relation with living conditions in early life [16, 18], whereas others have not [17, 33]. The 'fetal origin' hypothesis [37, 38] states that the risk of stroke is increased by maternal influences associated with poverty [37], a hypothesis, however, that is contested by others [39, 40]. Similarly, population-based studies have suggested that early life factors may be important determinants of the trends and geographical differences in mortality from cardiovascular disease in adults [13, 15, 36, 41-43]. For example, studies have shown a strong geographical correlation between mortality from various causes of death in adulthood and infant mortality around the time of birth, where infant mortality rate was taken to reflect living conditions in early life [13, 15, 36, 41-43] . One study observed that geographical differences in mortality from stroke in the late 20th century were correlated more strongly with infant mortality rates in the early 20th century than with current socio-economic conditions [13] .

Previous studies have reported declining trends of IHD for developed countries over recent decades [44-50], while the decline in stroke mortality rates between 1970 and 1990 slowed to a stop for both sexes and all ages [51]. Some studies assessed the effect of living conditions in early life on time trends (instead of geographical differences) in adult mortality [22, 52]. These studies focused on the question of whether time trends in adult mortality reflect cohort effects or period effects. A period effect is evident when a similar (approximately parallel) shift in rates is seen in each age group during a particular calendar period, while a cohort effect is manifested by age-specific rates that rise and fall in parallel when plotted against year of birth (cohort) [52]. Cohort effects would be suggestive of effects located in early life, but clear evidence for such effects was lacking in most studies [22].

In this paper, we present results of a population-based time-series study that aimed to describe trends in mortality between subsequent cohorts in relation to living conditions in early life of these cohorts. We assessed cohort-wise trends of ischemic heart disease (IHD) and stroke mortality of populations in seven European countries, and determined whether these trends were correlated with developments in infant mortality rate at the time of birth of the subsequent cohorts. We addressed three research questions: 1) What are the trends in age- and sex-specific mortality from IHD and stroke in seven European countries between 1950 and 1999? 2) What are the trends according to birth cohort? 3) Do these cohort-wise trends coincide with trends in infant mortality rates in subsequent cohorts from 1860 to 1939?

2.2. Methods

We obtained data on ischemic heart disease, stroke mortality and population at risk, by year of death (1950-1999), sex, and five-year age group for seven low-mortality European countries, i.e. Denmark, England & Wales, Finland, France, the Netherlands, Norway, and Sweden. For Denmark, Finland and Norway data were available only from 1951, and for Sweden, from 1952. For France, data were only available until the year 1997 and for Denmark, until 1998. The data were obtained from national statistical offices and related institutes. See Janssen et al., 2004, for more information [23].

In reconstructing mortality trends from IHD and stroke over the period from 1950 to 1999, we first ran up against the fact that the International Classification of Diseases (ICD-6 to ICD-10) had been revised five times during this same period. To reconcile these differences, we constructed a general concordance table, in which the different codes for stroke and for IHD in the successive ICD revisions were linked [23]. For IHD, we selected the ICD codes 420 and 422.1 for ICD-6 and ICD-7, 410-414 for ICD-8 and ICD-9, and I20-I25 for ICD-10. For cerebrovascular diseases we selected ICD codes 330-334 for ICD-6 and ICD-7, 430-434 and 436-438 for ICD-8 and ICD-9, and I60-I69 for ICD 10 [23, 53]. For IHD, the numbers of deaths for code 422.1 under ICD-6 and ICD-7 were not available for Finland until 1963, and Sweden until 1961. We estimated these on the basis of the ratio of the number of deaths from ischemic heart disease with and without 422.1, calculated for the first year in which 422.1 was coded.

Remaining mortality discontinuities - caused by the use of three-digit instead of four-digit codes and by incidental changes in coding rules – were identified and adjusted for in our analysis (see Janssen and Kunst (2004) for more information) [29]. We adjusted the person-years for the incidental changes in coding rules for stroke in 1956-58 for Finland, and for the generally applied coding changes in England and Wales between 1984 and 1992 [29]. We made adjustments for the mortality discontinuity in IHD due to the ICD revision from ICD-8 to ICD-9 in the Netherlands, and for the incidental changes in coding rules from 1970 onwards for Sweden [29].

Data on infant mortality rates (IMR), defined as the number of deaths during the first year of life per 1000 live-born babies, for the period 1860-1969 were obtained from Mitchell for most countries [54], and from Turpeinen for Finland [25].

In order to describe trends in mortality between 1950 and 1999, age-adjusted mortality rates by 10-year intervals were calculated using direct standardization, taking the age-specific person-years of each country in the 1950s as standard. For describing trends over time, we looked at two periods: from the 1950s to the 1970s (measured by age-adjusted mortality rate of 1970s

divided by the age-adjusted mortality rate of 1950s) and from the 1970s to the 1990s (measured in similar ways).

In order to describe mortality differences between birth cohorts 1860 to 1939, we analyzed the mortality data by means of a log-linear regression analysis (Poisson regression). The dependent variable was the number of deaths, with the person-years at risk as offset variable. We included age and cohort (one-year intervals in table 1, and five-year intervals in table 2 to 4) as independent variables. Table 3 illustrates the mortality rates in each five-year birth cohort relative to the mortality rates in cohort 1900-1904, thus enabling comparisons of the mortality rates between different cohorts to be made. These relative cohort mortality measures were derived from the parameter estimates of the cohort variable in the regression analysis.

Only age was controlled for in these cohort analyses. In subsequent analyses, however, we also controlled for 'drift', the common linear trend, and non-linear period effects [55, 56] and found basically the same patterns of cohort differences in mortality as those shown below.

Pearson correlation coefficients were calculated in order to quantify associations between cohort-specific mortality levels and the level of IMR of each birth cohort. These correlations were estimated by comparing cohorts within countries. In addition, a pooled analysis was made combining all birth cohorts for all countries together. We restricted all analyses to cohorts born between 1860 and 1939, thus excluding birth cohorts with too few deaths during the observation period. Additional analyses, with further restriction to birth cohorts born between 1875 and 1924, showed similar results to those reported below.

We used SPSS for Windows (10.1) package, Excel for Windows, and SAS 8.0.

2.3. Results

Table 2.1 shows changes in mortality according to period of death, comparing the 1950s to the 1970s and the 1970s to the 1990s. IHD mortality generally increased between the 1950s and 1970s in all countries for both men and women, except for women in France and Finland below 45 years. These increases were generally followed by a decline in IHD mortality in all countries between the 1970s and 1990s. The latter decreases were larger among younger people. Mortality from stroke declined from the 1950s to the 1990s in all age groups in most countries, often with larger declines in more recent decades.

Table 2.2 shows trends in mortality by year of birth from 1860 to 1939, subdivided into four segments, with each segment covering 20 years (1860 to 1879, 1880 to 1899, 1900 to 1919, and 1920 to 1939). Mortality from IHD generally increased with increasing year of birth between 1860 and 1899, at which point it started to decline. The reversal from increasing to decreasing

IHD levels was more marked in France, Finland and Norway than in other countries. In many countries, the decline started earlier among women than among men. Stroke showed a more consistent pattern of decreasing mortality in most populations, after initial increases in many countries for the birth cohorts 1860 to 1879. The rate of the decline in stroke mortality greatly differed according to birth period, country and sex, with mostly higher declines for the youngest birth cohorts.

Figure 2.1 shows the trends by 5-year birth cohort in IHD, stroke, and infant mortality. IHD mortality increased between successive cohorts up to those born in about 1900, and then started to decline. Increased stroke mortality levels were relatively stable in birth cohorts up to 1880, but declined rapidly in subsequent cohorts. IMR showed a general tendency to decline, especially after 1900, a tendency that started much later in some countries (e.g. Denmark and England & Wales) than in others (e.g. The Netherlands). The irregularities in the decline in IMR do not clearly correspond to similar irregularities in the decline in stroke.

Table 2.3 shows the correlation coefficients comparing the cohort-specific levels of IMR with mortality trends from stroke or IHD at adult age for the subsequent cohorts. A variable and sometimes inverse relationship between IHD mortality and infant mortality was found in the different countries. On the other hand, there was a significant and strong positive association across birth cohorts between IMR and stroke mortality at adult age. The correlation coefficients were 0.83 for Denmark and 0.93 or more for other countries. When all countries are pooled, and associations across countries are also taken into account, the overall correlation is large for stroke (0.72) but non-significant for IHD mortality.

In table 2.4, correlations across countries are calculated separately for each 5-year birth cohort. The relationship between stroke mortality and infant mortality rate was slightly positive when comparing countries for birth cohorts born before 1900. However, for birth cohorts born after 1900 this association was slightly negative. The inter-country association between IHD and infant mortality was negative in all birth cohorts, with significant negative correlations for birth cohorts born before 1895. Thus, countries with higher IMR before 1895 had lower IHD mortality rates among the same birth cohorts at adult ages.

2.4. Discussion

There have been relatively few studies on the possible impact of early life circumstances on trends in mortality from cardiovascular diseases within national populations. We performed a time series analysis in which special attention was paid to cohort patterns. We studied trends in IHD and stroke in relation to IMR in birth cohorts born between 1860 and 1939 in seven low-mortality European countries, observing a general cohort-wise decline in mortality from stroke in all countries and in both sexes, compared to an

epidemic pattern of change for IHD. While the trends in IHD mortality were not strongly correlated with the infant mortality rate in subsequent cohorts, strong and positive correlations were observed for stroke.

However, irregularities in trends in IMR between 1860 and 1940 were not reflected in similar irregularities in trends in stroke in later years. The irregularities in secular trends in IMR reflect true and important developments in the past, which might have been reflected in the mortality rates of affected birth cohorts during their later life. However, such lasting effects are not observed in our study. In addition, inter-country variations in IMR levels in the past had no strong positive correlations with cohort levels of stroke mortality at adult age.

We should stress that our objectives, empirical analyses, and inferences all refer to the same level of analyses, i.e. national populations. In this type of analysis, there is a risk of ecological fallacy [57]. However, this fallacy would be committed only if inferences were to be made towards the individual level. We have refrained from making such inferences, because trends in stroke mortality at the national level may strongly be influenced by factors that may have little effect at the individual level.

The mortality and population data used in this study come from data sources that are known to be of good quality [58-60]. Any problems with the coverage or completeness of death registries or population registrations are likely to have had no or minimal effects on our results. We made a special effort to deal with ICD- and other coding related changes affecting mortality trends from IHD and stroke that are often neglected in other studies. Even though some residual effects of coding problems could not be excluded, we are confident that these problems did not affect the results to any substantial extent [23, 53].

The results for the oldest 5-year cohorts (i.e. birth cohort 1860-1864) should be interpreted cautiously, as only the mortality of those aged 85 years and over could be studied. Therefore, no valid comparisons can be made between the mortality level of this cohort and the mortality levels of younger cohorts, in which the mortality at younger ages could also be studied. Greater weight should therefore be given to results for the birth cohorts that could be followed across a longer age range, i.e. cohorts born after 1870 or 1875.

Table 2.1 – Trends in mortality from ischemic heart disease and stroke in seven European countries between the 1950s and the 1990s, by age and sex

Country	Age Group	Rate ratio comparing second to first period [a]							
		IHD				Stroke			
		Male		Female		Male		Female	
		1970s to 1950s	1990s to 1970s	1970s to 1950s	1990s to 1970s	1970s to 1950s	1990s to 1970s	1970s to 1950s	1990s to 1970s
Denmark	<45	1.8	0.5	2.1	0.4	1.1	0.9	1.2	0.9
	45-64	1.6	0.5	1.3	0.6	0.7	0.8	0.5	0.8
	65-79	1.6	0.6	1.1	0.6	0.6	0.7	0.4	0.7
	80+	1.7	0.7	1.4	0.6	0.6	0.8	0.6	0.8
England & Wales	<45	1.7	0.4	1.2	0.5	0.9	0.6	1.0	0.6
	45-64	1.5	0.5	1.1	0.7	0.7	0.5	0.7	0.4
	65-79	1.2	0.7	1.0	0.8	0.8	0.5	0.8	0.5
	80+	1.1	0.8	1.0	0.8	0.9	0.6	1.1	0.6
Finland	<45	1.2	0.3	0.8	0.4	1.1	0.4	0.9	0.4
	45-64	1.6	0.4	1.2	0.4	0.8	0.5	0.6	0.4
	65-79	1.5	0.7	1.4	0.7	0.8	0.6	0.6	0.5
	80+	1.5	1.0	1.3	1.0	0.8	0.6	0.8	0.6
France	<45	1.8	0.8	0.7	0.8	0.7	0.6	0.6	0.6
	45-64	1.4	0.6	1.0	0.5	0.6	0.4	0.4	0.4
	65-79	1.6	0.7	1.5	0.6	0.7	0.4	0.6	0.3
	80+	2.2	1.0	2.4	1.0	1.0	0.5	1.0	0.5
Netherlands	<45	2.4	0.5	1.4	0.7	1.3	0.6	1.6	0.7
	45-64	2.0	0.5	1.1	0.7	0.9	0.6	0.7	0.5
	65-79	1.6	0.6	1.1	0.6	0.8	0.6	0.7	0.5
	80+	1.4	0.8	1.2	0.7	0.8	0.7	0.8	0.7
Norway	<45	2.0	0.5	1.2	0.7	1.2	0.5	1.3	0.5
	45-64	1.8	0.5	1.2	0.7	0.8	0.6	0.6	0.5
	65-79	1.8	0.7	1.3	0.6	0.9	0.6	0.8	0.5
	80+	1.8	0.8	1.5	0.7	1.0	0.7	1.0	0.6
Sweden	<45	1.7	0.6	1.4	0.8	0.9	0.5	0.9	0.4
	45-64	1.5	0.5	1.1	0.6	0.7	0.6	0.4	0.5
	65-79	1.6	0.6	1.1	0.5	0.6	0.7	0.5	0.6
	80+	1.5	0.6	1.2	0.5	0.7	0.8	0.7	0.8

[a]. Calculated as standardized death rate of the second period divided by standardized death rate of the first period

Table 2.2- Trends in mortality from ischemic heart disease and stroke over subsequent twenty-year birth cohorts from 1860 to 1939 in seven European countries, by sex

Country	Birth cohorts	Annual change in mortality (%) IHD Male	IHD Female	Stroke Male	Stroke Female
Denmark	1860-1879	+3.76 *	+4.30 *	-0.79 *	+0.13 *
	1880-1899	-0.14*	-0.22 *	-3.02 *	-4.21 *
	1900-1919	-0.35 *	-1.22 *	-1.14 *	-1.72 *
	1920-1939	-2.90 *	-1.48 *	-0.43 *	-0.91 *
England & Wales	1860-1879	-0.38 *	-0.12 *	+1.12 *	+1.59 *
	1880-1899	+0.10 *	-0.96 *	-3.06 *	-3.27 *
	1900-1919	-0.05 *	-0.43 *	-2.02 *	-2.18 *
	1920-1939	-2.96 *	-2.19 *	-3.00 *	-3.58 *
Finland	1860-1879	+2.41 *	+2.38 *	+1.78 *	+2.10 *
	1880-1899	+1.22 *	+0.40 *	-3.47 *	-4.64 *
	1900-1919	+0.05	-1.05 *	-1.65 *	-2.61 *
	1920-1939	-4.69 *	-4.80 *	-2.63 *	-4.11 *
France	1860-1879	+5.90 *	+7.57 *	+2.48 *	+3.19 *
	1880-1899	+1.80 *	+1.13 *	-3.82 *	-4.03 *
	1900-1919	-0.49 *	-2.23 *	-2.91 *	-4.01 *
	1920-1939	-1.75 *	-1.94 *	-3.37 *	-3.82 *
Netherlands	1860-1879	-0.16 *	+0.65 *	-0.26 *	+0.36 *
	1880-1899	+3.15 *	+0.80 *	-2.64 *	-3.94 *
	1900-1919	+0.80 *	-0.55 *	-1.45 *	-2.52 *
	1920-1939	-1.69 *	+0.83 *	-1.58 *	-1.44 *
Norway	1860-1879	+3.41 *	+4.27 *	+1.64 *	+1.95 *
	1880-1899	+0.83 *	-1.37 *	-2.66 *	-3.64 *
	1900-1919	-0.14 *	-1.22 *	-1.54 *	-2.53 *
	1920-1939	-2.80 *	-1.51 *	-2.08 *	-2.97 *
Sweden	1860-1879	+1.99 *	+2.87 *	-0.39 *	+1.11*
	1880-1899	-0.36 *	-2.82 *	-2.83 *	-3.78 *
	1900-1919	-0.69 *	-1.93 *	-1.35 *	+2.59 *
	1920-1939	-2.42 *	-1.50 *	-2.22 *	-3.10 *

* Trends different from 0 with statistical significance ($p < 0.01$)

Table 2.3- Correlation between trends in IHD or stroke mortality at adult ages and IMR among the birth cohorts from 1860 to 1939 in seven European countries

Country	Sex	Pearson correlation coefficient (95% CI)	
		IHD and IMR	Stroke and IMR
Denmark	Total	0.78 (0.46,0.92)	0.83 (0.57,0.94)
	Male	0.42 (-0.10,0.76)	0.82 (0.55,0.94)
	Female	0.89 (0.70,0.96)	0.84 (0.59,0.94)
England & Wales	Total	0.91 (0.76,0.97)	0.93 (0.80,0.97)
	Male	0.87 (0.65,0.95)	0.93 (0.80,0.98)
	Female	0.94 (0.84,0.98)	0.93 (0.80,0.97)
Finland	Total	0.28 (-0.27,0.69)	0.95 (0.87,0.99)
	Male	0.08 (-0.45,0.57)	0.97 (0.91,0.99)
	Female	0.54 (0.04,0.83)	0.95 (0.86,0.98)
France	Total	-0.20 (-0.64,0.32)	0.95 (0.85,0.98)
	Male	-0.32 (-0.70,0.21)	0.95 (0.87,0.98)
	Female	0.17 (-0.35,0.62)	0.94 (0.84,0.98)
Netherlands	Total	-0.86 (-0.95,-0.63)	0.97 (0.92,0.99)
	Male	-0.86 (-0.95,-0.63)	0.97 (0.92,0.99)
	Female	-0.64 (-0.86,-0.21)	0.97 (0.92,0.99)
Norway	Total	0.23 (-0.30,0.65)	0.98 (0.93,0.99)
	Male	-0.18 (-0.62,0.34)	0.98 (0.94,0.99)
	Female	0.62 (0.17,0.85)	0.98 (0.93,0.99)
Sweden	Total	0.87 (0.66,0.95)	0.99 (0.96,1.00)
	Male	0.55 (0.07,0.82)	0.99 (0.96,1.00)
	Female	0.92 (0.77,0.97)	0.98 (0.94,0.99)
All Countries	Total	-0.08 (-0.55,0.43)	0.72 (0.34,0.90)
	Male	-0.18 (-0.62,0.35)	0.72 (0.36,0.90)
	Female	0.07 (-0.44,0.55)	0.72 (0.34,0.89)

CI = Confidence Interval

Table 2.4- Correlation between international variations in IHD/Stroke mortality at adult ages and IMR for the birth cohorts from 1875 to 1925

Birth cohort	Pearson correlation coefficient (95% CI)	
	IHD and IMR	Stroke and IMR
1875-1879	-0.57 (-0.83,-0.11)	0.14 (-0.38,0.59)
1880-1884	-0.65 (-0.86,-0.22)	0.18 (-0.35,0.62)
1885-1889	-0.66 (-0.87,-0.24)	0.05 (-0.45,0.54)
1890-1894	-0.62 (-0.85,-0.18)	0.07 (-0.44,0.55)
1895-1899	-0.24 (-0.66,0.29)	0.31 (-0.22,0.70)
1900-1904	-0.31 (-0.70,0.22)	-0.10 (-0.57,0.41)
1905-1909	-0.24 (-0.66,0.29)	-0.17 (-0.61,0.36)
1910-1914	-0.18 (-0.62,0.34)	-0.18 (-0.62,0.34)
1915-1919	-0.20 (-0.63,0.33)	-0.06 (-0.54,0.45)
1920-1924	-0.23 (-0.65,0.30)	-0.16 (-0.60,0.37)

CI = Confidence Interval

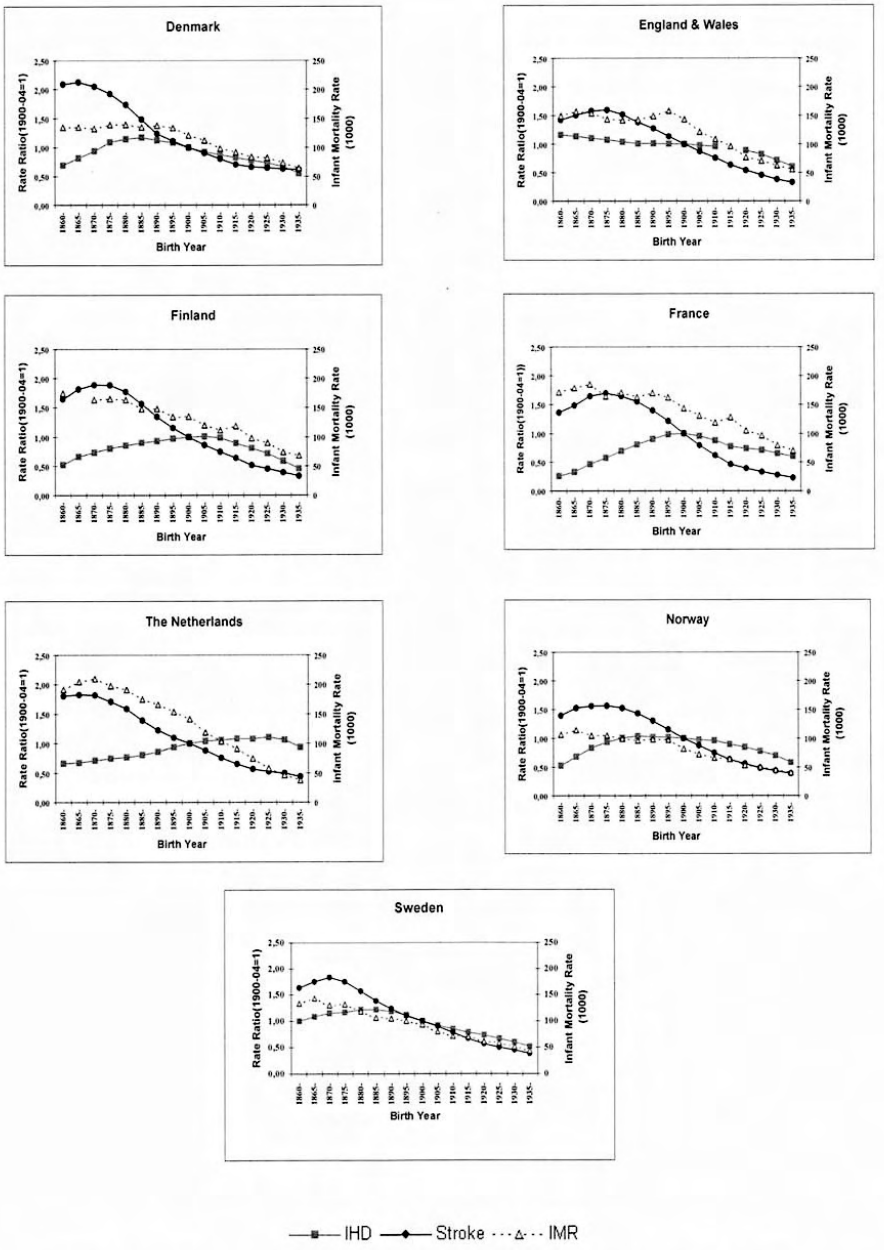

Figure 2.1- Trends in IMR and in the mortality rate ratio of IHD and stroke at adult ages, in five-year birth cohorts from 1860 to 1939

The question is whether different results would have been obtained if the competing causes of death phenomenon had been taken into account. Due to the "competing causes of death" problem, the level of mortality from both causes of death may be lower than it would have been without competition for the lives of people with common risk factors. It is impossible to correct for this common phenomenon in our trend analysis [61]. The overall effect would have been an increase in the number of deaths observed for either cause of death, especially at the oldest ages. However, recent analyses have suggested that time trends in old-age mortality may not be affected very much by selection (or competition) effects for mortality at earlier ages [62]. Peeters et al, furthermore, concluded that there is no support for the hypothesis that increases in the number of people with cardiovascular disease, as a consequence of improvements in cardiovascular disease survival, explain the observed leveling off of the decline in the rate of stroke mortality [52].

The outcome measures in our study are mortality rates for IHD and stroke according to birth cohort and country. Differences in mortality rates by place and over time are the result of a complex interplay of many factors. In our analysis of associations with IMR, we were not able to control for potential confounders. For example, the cohort patterns of IHD mortality, which peaked among birth cohorts born around 1900, might be determined by smoking and other factors related to later phases of the life course. Similarly, the inverse (instead of positive) correlations between IMR and stroke in the cross-national analyses might have been confounded by cross-national differences in recent factors such as modern diet, alcohol consumption patterns, or hypertension treatment. Given this potential for confounding, the correlations observed in this study should be regarded as suggestions to be confirmed in future population-based studies.

The secular trends in IHD in the second half of the 20th century (an epidemic pattern) were very different from the steady decline in stroke. The factors that explain the different trends for IHD in comparison to stroke are not fully understood, but may be related to a relatively greater impact of smoking and serum cholesterol on IHD mortality compared to stroke mortality. Although IHD and stroke share key risk factors such as high blood pressure, tobacco use, and overweight [63, 64], the strength and directions of the associations may be different for the two diseases. The discrepancy in trends for IHD and stroke warns against too strong statements regarding the effect of early living conditions.

Several reports have argued that declining IHD and stroke mortality rates are attributable to improved survival rates rather than to decreased incidence rates [65-69]. The declining case fatality [70] may be due to advances in diagnosis and treatment [71], including rapid dissemination of CT and MRI technology since 1970s [72]. Studies on 10-year trends in the WHO MONICA populations show that two thirds of the decline in stroke mortality remains unexplained after

control for classical risk factors [73]. A part of the unexplained trends might be due to changes in other risk factors, such as socioeconomic status, food consumption, or different combinations of some or all of these [73]. Early life exposures might be one of the factors that contribute to trends in stroke mortality.

By understanding the process of growth development, and by scrutinizing the growth process, factors in early life that influence susceptibility to later disease can be identified [74]. Van Rossum reported that risk factors earlier in life may be of importance in stroke [75]. Areas of England and Wales with high stroke mortality were characterized in the past by poor living standards, demonstrated by high infant and maternal mortality rates and short stature in the adult population [76]. Stroke may be related to maternal influences associated with poverty; this suggestion is supported by recent findings that rates of stroke in adult life are higher among people who had low birth weight [37]. Reduced fetal growth, i.e. the reduction in growth which begins early in gestation, is associated with increased risk of cardiovascular disease [76].

To conclude, we observed a strong relationship between cohort-trends in stroke mortality and cohort-trends in infant mortality in European low-mortality countries. Although determining the exact contribution of living conditions in early life to national trends in stroke mortality remains difficult to ascertain, this association is in line with evidence from individual level studies. It suggests that living conditions earlier in life may have had an effect on the mortality experience of national cohorts, and that changes over time in these living conditions may have contributed to the secular decline in stroke mortality. We conclude that cohort patterns should be considered when studying secular trends in mortality from cardiovascular diseases. Future studies on the role of early life circumstances should be sensitive to differences between countries and between historical periods in the potential impact of these circumstances.

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Trends in stomach cancer mortality in relation to living conditions in childhood. A study among cohorts born between 1860 and 1939 in seven European countries

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Abstract

Aim: To assess whether secular trends in stomach cancer mortality were correlated with trends in infant mortality rate (IMR) or gross domestic product (GDP).

Methods: Data from seven European countries were analyzed. We used Poisson regression to describe mortality trends among birth cohorts of 1865-1939 and correlation coefficients to determine associations with IMR/GDP.

Results: Large differences were observed between birth cohorts in mortality from stomach cancer. In each country, these cohort differences were closely related to IMR/GDP levels at birth time. However, stronger associations were observed with measures of living conditions during later life. In comparisons between countries, stomach cancer mortality rates were not consistently related to national levels of IMR/GDP.

Conclusion: General living conditions in childhood don't seem to have had a predominant effect on secular trends in stomach cancer mortality. The mortality decline is likely to be related to more specific factors, such as declining H. pylori prevalence.

Key Words: Europe, Mortality decline, stomach neoplasm, Infant mortality, Gross national product

3.1. Introduction

In spite of declining incidence rates worldwide, stomach cancer is the second most important cause of death from cancer [7]. Previous studies confirm the importance of "environment" in early life in determining the risk for stomach cancer [7, 19]. Furthermore, a number of studies have shown a strong geographical correlation between mortality from stomach cancer in adulthood and infant mortality around the time of birth [14, 36]. Also, mortality from stomach cancer showed consistent inverse socio-economic gradients and an association with socio-economic circumstances in childhood [77].

Time trends of stomach cancer differ between populations and the role of living conditions on trends is not yet fully understood [20]. To our knowledge, no study on trends in stomach cancer focused on birth cohorts and looked at measures of their association with living conditions in early life.

To provide new evidence on the role of living conditions in early childhood on trends in stomach cancer mortality, we conduct a population-based time-series study. The main hypothesis of our study was that living conditions in childhood are associated with trends in stomach cancer mortality in national populations. We used data on stomach cancer mortality and population at risk for seven low-mortality European countries. Using these data, we tested four specific research hypotheses: 1) Trends in mortality from stomach cancer follow a cohort pattern, with lower mortality among younger cohorts. 2) Cohort trends in stomach cancer mortality correspond closely to cohort trends in living conditions in childhood. 3) For each cohort, differences between countries in stomach cancer mortality are closely correlated to differences in living conditions in childhood. 4) Stomach cancer mortality trends are associated with trends in living conditions in childhood rather than with trends in living conditions in adult life.

3.2. Materials and Methods

We obtained data on stomach cancer mortality and population at risk, by year of death (1950-1999), sex, and five-year age groups for seven low-mortality European countries, i.e. Denmark, England & Wales, Finland, France, the Netherlands, Norway, and Sweden. For Denmark, Finland and Norway data were available from 1951, and for Sweden from 1952. Data for France were available until 1997 and data for Denmark until 1998. The data were obtained from national statistical offices and related institutes. Compared to the mortality information available in the WHO Mortality Bank (http://www.euro.who.int/InformationSources/Data/20050117_1), our data went further back in time, and made a more detailed distinction among upper age groups, which is essential for the study of mortality by birth cohort. For stomach

cancer, we included code 151 for revisions 6, 7, 8, and 9 of the International Classification of Diseases (ICD), and code C16 for ICD-10 [23].

Data on infant mortality rates (IMR), defined as the number of deaths during the first year of life per 1000 live-born babies, for the period 1860-1969, were obtained from international compilations [78], and for Finland from a national publication [25].To reconstruct trends in real national GDP, i.e. GDP expressed at constant 1995 prices in millions of national currency units, between 1865 and 1939, we used historical national accounts data [26]. For the Netherlands, these historical data were available only from 1900 onwards, and for the earlier years data on national accounts from Statistics Netherlands were used [27]. Further detail on the reconstruction of the time series for GDP are given elsewhere [79].

In order to describe mortality differences between birth cohorts, we analyzed the mortality data by means of a log-linear regression analysis (Poisson regression). The dependent variable was the number of deaths, with the person-years at risk as offset variable. As independent variables, we included age and cohort (one-year intervals in table 1, and five-year intervals in table 2 to 4). In tables 2 to 4, we expressed mortality rates of each five-year birth cohort relative to the mortality rates of the birth cohort 1900-1904, thus enabling comparisons of the mortality rates between different cohorts. These relative cohort mortality measures were derived from the parameter estimates of the cohort variable in the regression analysis.

In these cohort analyses, control was made for age only. In additional analyses, we checked whether similar patterns would be observed when also controlling for the 'drift', the common linear trend, and non-linear period effects [55, 56]. These additional analyses showed basically the same patterns of cohort differences in mortality as those shown below.

Pearson correlation coefficients were calculated in order to quantify associations between cohort-specific mortality rates and the level of infant mortality rate or GDP of each birth cohort. These correlations were estimated by comparing cohorts within countries. In addition, a pooled analysis was carried out combining all birth cohorts for all countries together. We restricted all analyses to cohorts born between 1860 and 1939, thus excluding birth cohorts with too few deaths during the observation period. Additional analyses, with further restriction to birth cohorts born between 1865 and 1924 showed similar results as those reported below. We used SPSS for Windows (10.1) package, Excel for Windows, and SAS 8.0.

3.3. Results

Mortality of stomach cancer decreased over the successive cohorts from 1860 to 1939 (Table 3.1 and Figure 3.1). For Finnish men, and in France, however, the decline started later, i.e. from birth cohorts 1880 onwards. The

decline in stomach cancer over successive cohorts is generally stronger among women than among men.

Figure 3.2 shows the trends in infant mortality (IMR) by five-year periods. The patterns were varied until about 1895. From 1895 onwards, a general decline in IMR emerged. In comparison with the mortality trends for stomach cancer, the declining trends in IMR are sharper and more stable.

Figure 3.3 presents the trends in GDP at birth by five-year periods. An overall increase in GDP at birth can be observed for all countries. During 1915-1919 a decline in GDP at birth occurred, except for England and Wales. The increasing trends for GDP at birth were however not simultaneous to the declining mortality trends for stomach cancer. Moreover, irregularities in trends in GDP and stomach cancer mortality did not coincide.

Table 3.2 shows the correlation coefficients comparing the levels of IMR and GDP at birth with mortality from stomach cancer at adult age for the same cohorts. There was a significant strong positive association (correlation coefficients ranging from 0.70 to 0.98) between stomach cancer and IMR in all countries. The association between stomach cancer mortality and GDP at birth was strongly negative, with correlation coefficients ranging from -0.98 to -0.80. When the different countries are pooled, the overall correlation was positive for IMR (0.71) and negative for GDP at birth (-0.63). The correlation coefficients were generally higher among men than among women.

In table 3.3, correlations across countries between stomach cancer mortality and IMR and GDP at birth are calculated for each five-year birth cohort separately. The relationship between stomach cancer mortality and IMR was positive for cohorts born after 1875 (correlation coefficients ranging from 0.04 to 0.55), and negative for cohorts born before (correlation coefficients ranging from –0.55 to –0.29). The association between stomach cancer mortality and GDP at birth was in general negative but variable for the different birth cohorts (correlation coefficients ranging from –0.44 to 0.06).

Table 3.4 shows the correlation coefficients between stomach cancer and IMR and GDP at birth from the pooled analysis. In this table, IMR and GDP are not only measured for the time of birth of each cohort, but also for older ages of the cohorts. There was a significant strong positive association between stomach cancer and infant mortality rate as measured for different ages of the cohorts (correlation coefficients ranging from 0.70 to 0.85). The associations were stronger with the IMR that applied to the time that a cohort was relatively old. There was a strong negative association between stomach cancer mortality and GDP at different ages of the cohort (correlation coefficients ranging from -0.92 to -0.62). The associations were stronger for GDP measured at the older ages.

3.4. Discussion

In this study, the well-known cohort-wise decline in stomach cancer in seven European countries has been confirmed. For each sex and country, we

observed large differences between cohorts in mortality rates from stomach cancer. These differences were closely related to levels of IMR and GDP at the time of birth. Strong correlations between mortality trends and IMR and GDP were observed for each sex and country.

However, part of our additional findings do not support our basic hypothesis that improvements in general living conditions in childhood had driven the secular decline in stomach cancer mortality in western European countries. First, stronger associations were observed with measures of living conditions during later phases of life instead of early life. Second, past irregularities in trends in living conditions (which reflect important historical phenomena such as deep economic crises) were not associated with similar irregularities in trends in stomach cancer mortality in later life. Finally, in comparisons between countries (instead of between birth cohorts), we did not observe a consistent association between stomach cancer mortality rates and national levels of IMR or GDP.

3.4.1. Evaluation of data and methods

The mortality and population data used in this study comes from data sources that are known to have good quality [58-60]. Any problems with the coverage or completeness of death registries or population registries are likely to have no or minimal effects on our results.

We should stress that our objectives, empirical analyses, and inferences all refer the same level of analyses, i.e. national populations. In this type of analysis, there is a risk of ecological fallacy [57] but this fallacy will only be committed if inferences towards the individual level would be made. We refrain from making such inferences and we warn that trends in stomach cancer mortality at the national level may strongly be influenced by factors that are not necessarily the most important determinants of stomach cancer at the individual level.

The outcome measures in our study were rates of stomach cancer according to birth cohort and country. Differences in mortality rates by place and over time are the result of a complex interplay of many factors. In our analysis of associations with IMR and GDP, we were not able to control for potential confounders. For example, the inverse (instead of positive) correlations of stomach cancer mortality with IMR and GDP in the cross-national analyses might have been confounded by cross-national differences in factors such as modern diet and health care services. Given this potential for confounding, the correlations observed in this study should be regarded with caution.

In our analysis, the IMR and GDP were used as indicators of general conditions of living in different periods. These two indicators were used because of the availability and comparability of data for seven European countries over a long period of time. For a possible alternative indicator, body length, continuous

historical time series were only available for four countries [80]. It should be acknowledged that both IMR and GDP are only approximate indicators of the concept of "general living conditions". None the less, the IMR is one of the most important indicators of social development. Reidpath concluded that the IMR is an important indicator of health for whole populations, as structural factors affecting the health of entire populations also have an impact on the mortality rate of infants [81]. The correspondence between the findings for IMR and those for GDP lends support to our general conclusion that improvements in general living conditions in childhood are not strongly related to the secular decline in stomach cancer mortality in western European countries.

3.4.2. Interpretation

Our findings of declining patterns of stomach cancer correspond well with the results of previous studies [7, 14, 19, 36, 82]. Differences between birth cohorts in rates of mortality from stomach cancer were also observed in studies that controlled for period effects [23, 83].

The relation between adverse childhood social circumstances and higher adulthood mortality risk has been demonstrated in several studies [19, 82, 84]. Individual-level studies showed that childhood socioeconomic position influences stomach cancer mortality in later life [85]. The association between childhood social circumstances and mortality probably comes about through a variety of processes [86]. Migrant studies also suggest the importance of environment in early life in determining the risk of stomach cancer [7].

The etiology of stomach cancer is linked to environmental factors, including nutrition in childhood (e.g.. salt consumption, vitamin C intake) [87], *Helicobacter pylori* infection [7, 88], and interaction between these factors [89]. Infection with *Helicobacter pylori* during infancy and childhood offers a plausible mechanism to explain the association between poor childhood circumstances and stomach cancer [90]. Favorable developments in childhood nutrition might have contributed to the secular decline in stomach cancer mortality.

It is important to recognize that our measures of general living conditions in childhood (IMR and GDP) cannot measure in detail all specific elements that may be relevant for stomach cancer. In case of H. pylori, we would need to acquire data on the prevalence of H. pylori infection in childhood in the different birth cohorts. These data were not available for any of the countries considered. Accepting that past trends in stomach cancer mortality may be strongly determined by past trends in the incidence of H. pylori infection, our results suggest that the latter trends are not closely correlated with past trends in IMR and GDP.

Some of our results suggest that secular trends in stomach cancer are largely determined by changes in adult socioeconomic circumstances and

lifestyles, rather than childhood [91]. For example, the marked cohort pattern of stomach cancer mortality, which peaked among birth cohorts born around 1875, might be determined by cohort-specific trends in smoking, alcohol consumption and other factors related to later phases of the life course. Similarly, improvements during the 20th century in environment and nutrition may have resulted in a gradually lower incidence of stomach cancer, while more accessible and effective facilities for cancer therapy may have helped to reduce its case fatality [91].

As a conclusion, our results do not provide sufficient support for our main hypothesis that living conditions in childhood have a predominant effect on secular trends in stomach cancer mortality in national populations. Trends in stomach cancer mortality follow a cohort pattern, but this pattern is not consistently related to indicators of general living conditions in childhood. Trends in stomach cancer mortality seem to be determined by a set of more specific determinants that might operate in adult life as well as early life. Future studies should determine the contribution of more specific factors, such as H. pylori infection, instead of general living conditions in early life.

Table 3.1-Annual change in mortality from stomach cancer in birth cohorts born between 1860 and 1939 in seven European countries, by country, 20-year cohort group and sex

Country	Cohort	Annual change in mortality (%)		
		Male	**Female**	**Total**
Denmark	1860-1879	-2.49*	-4.18*	-3.60*
	1880-1899	-3.90*	-5.64*	-4.85*
	1900-1919	-4.65*	-4.72*	-4.59*
	1920-1939	-2.83*	-1.92*	-2.51*
England & Wales	1860-1879	-0.16	-1.39*	-1.38*
	1880-1899	-1.11*	-2.73*	-1.94*
	1900-1919	-2.85*	-3.70*	-2.91*
	1920-1939	-4.71*	-4.39*	-4.59*
Finland	1860-1879	+0.88	-0.71	-0.43
	1880-1899	-3.75*	-5.00*	-4.70*
	1900-1919	-5.36*	-5.40*	-5.34*
	1920-1939	-4.98*	-3.86*	-4.36*
France	1860-1879	+1.10*	+0.67*	+0.46*
	1880-1899	-2.69*	-3.72*	-3.18*
	1900-1919	-4.08*	-5.28*	-4.33*
	1920-1939	-3.43*	-3.82*	-3.49*
Netherlands	1860-1879	-1.43*	-2.10*	-1.92*
	1880-1899	-1.74*	-3.33*	-2.72*
	1900-1919	-1.47*	-2.97*	-1.97*
	1920-1939	-1.89*	-1.39*	-1.55*
Norway	1860-1879	-2.46*	-4.15*	-3.56*
	1880-1899	-3.06*	-4.28*	-3.71*
	1900-1919	-3.77*	-4.11*	-3.84*
	1920-1939	-4.04*	-3.57*	-3.83*
Sweden	1860-1879	-0.90	-2.73*	-2.11*
	1880-1899	-3.59*	-4.98*	-4.31*
	1900-1919	-4.19*	-4.38*	-4.19*
	1920-1939	-4.12*	-3.08*	-3.76*

* Trends different from 0 with statistical significant ($p < 0.01$).

Table 3.2- Correlation between stomach cancer mortality and indicators of living conditions at the time of birth, among 16 cohorts (born between 1860 and 1939 and followed for mortality in 1950-1999), per country and sex

Country	Sex	Pearson correlation coefficient (95% CI)	
		With IMR	With GDP
Denmark	Total	0.74 (0.39,0.91)	-0.83 (-0.94,-0.58)
	Male	0.81 (0.53,0.93)	-0.88 (-0.96,-0.68)
	Female	0.70 (0.32,0.89)	-0.80 (-0.93,-0.51)
England & Wales	Total	0.89 (0.71,0.96)	-0.97 (-0.99,-0.90)
	Male	0.96 (0.88,0.99)	-0.99 (-1.00,-0.84)
	Female	0.86 (0.63,0.95)	-0.94 (-0.98,-0.84)
Finland	Total	0.81 (0.51,0.94)	-0.98 (-0.99,-0.94)
	Male	0.77 (0.44,0.92)	-0.97 (-0.99,-0.92)
	Female	0.83 (0.56,0.94)	-0.98 (-0.99,-0.93)
France	Total	0.92 (0.79,0.97)	-0.93 (-0.97,-0.80)
	Male	0.93 (0.81,0.98)	-0.94 (-0.98,-0.83)
	Female	0.91 (0.77,0.97)	-0.92 (-0.97,-0.77)
Netherlands	Total	0.91 (0.74,0.97)	-0.86 (-0.95,-0.62)
	Male	0.94 (0.82,0.98)	-0.90 (-0.96,,-0.73)
	Female	0.89 (0.71,0.96)	-0.84 (-0.94,-0.58)
Norway	Total	0.87 (0.66,0.95)	-0.84 (-0.94,-0.58)
	Male	0.90 (0.74,0.97)	-0.88 (-0.96,-0.68)
	Female	0.85 (0.62,0.95)	-0.81 (-0.93,-0.52)
Sweden	Total	0.96 (0.90,0.99)	-0.90 (-0.96,-0.73)
	Male	0.98 (0.94,0.99)	-0.94 (-0.98,-0.82)
	Female	0.94 (0.84,0.98)	-0.87 (-0.95,-0.65)
All Countries	Total	0.71 (0.34,0.89)	-0.63 (-0.86,-0.20)
	Male	0.74 (0.38,0.90)	-0.65 (-0.87,-0.23)
	Female	0.70 (0.32,0.89)	-0.62 (-0.85,-0.18)

CI, Confidence Interval.

Table 3.3- Correlation between stomach cancer mortality and indicators of living conditions at the time of birth, among seven European countries, per birth cohort (followed for mortality in 1950-1999), men and women combined

Birth Cohort	Pearson correlation coefficient (95% CI)	
	With IMR	With GDP
1860-1864	-0.55 (-0.82,-0.08)	a
1865-1869	-0.46 (-0.78,0.05)	-0.26 (-0.67,0.27)
1870-1874	-0.29 (-0.70,0.24)	-0.02 (-0.53,0.48)
1875-1879	0.04 (-0.47,0.52)	-0.23 (-0.65,0.30)
1880-1884	0.53 (0.04,0.81)	-0.44 (-0.77,0.07)
1885-1889	0.40 (-0.11,0.75)	-0.40 (-0.75,0.12)
1890-1894	0.39 (-0.13,0.74)	-0.31 (-0.70,0.22)
1895-1899	0.35 (-0.18,0.72)	-0.33 (-0.71,0.19)
1900-1904	0.49 (-0.01,0.79)	-0.17 (-0.62, 0.35)
1905-1909	0.46 (-0.04,0.78)	-0.17 (-0.62,0.35)
1910-1914	0.55 (0.08,0.82)	-0.17 (-0.61,0.36)
1915-1919	0.54 (0.06,0.82)	0.06 (-0.45,0.54)
1920-1924	0.40 (-0.12,0.75)	-0.29 (-0.69,0.24)
1925-1929	0.36 (-0.17,0.72)	-0.29 (-0.68,0.24)
1930-1934	0.35 (-0.18,0.72)	-0.33 (-0.71,0.19)
1935-1939	0.53 (0.04,0.81)	-0.34 (-0.72,0.19)

CI, Confidence Interval.

a Data for GDP were not available for all countries.

Table 3.4- Correlation between stomach cancer mortality and indicators of living conditions at different ages, among seven countries and 16 cohorts (born between 1860 and 1939 and followed for mortality in 1950-1999), per sex

Age [a]	Sex	Pearson correlation coefficient (95% CI)	
		With IMR	With GDP
0-4	Total	0.71 (0.34,0.89)	-0.63 (-0.86,-0.20)
	Male	0.74 (0.38,0.90)	-0.65 (-0.87,-0.23)
	Female	0.70 (0.32,0.89)	-0.62 (-0.85,-0.18)
5-14	Total	0.77 (0.44,0.92)	-0.66 (-0.87,-0.24)
	Male	0.79 (0.48,0.92)	-0.68 (-0.88,-0.28)
	Female	0.76 (0.42,0.91)	-0.64 (-0.86,-0.22)
15-24	Total	0.81 (0.53,0.93)	-0.73 (-0.90,-0.36)
	Male	0.82 (0.54,0.93)	-0.75 (-0.91,-0.41)
	Female	0.81 (0.52,0.93)	-0.71 (-0.89,-0.32)
25-34	Total	0.84 (0.59,0.94)	-0.76 (-0.91,-0.43)
	Male	0.84 (0.58,0.94)	-0.79 (-0.93,-0.49)
	Female	0.84 (0.59,0.94)	-0.74 (-0.90,-0.39)
35-44	Total	0.85 (0.62,0.95)	-0.77 (-0.91,-0.44)
	Male	0.84 (0.59,0.94)	-0.80 (-0.93,,-0.51)
	Female	0.85 (0.62,0.95)	-0.74 (-0.90,-0.39)
45-54	Total	0.85 (0.61,0.95)	-0.81 (-0.93,-0.52)
	Male	0.83 (0.58,0.94)	-0.85 (-0.95,-0.60)
	Female	0.85 (0.61,0.95)	-0.78 (-0.92,-0.47)
55-64	Total	0.83 (0.56,0.94)	-0.86 (-0.95,-0.63)
	Male	0.81 (0.52,0.93)	-0.89 (-0.96,-0.71)
	Female	0.84 (0.58,0.94)	-0.83 (-0.94,-0.58)
65 +	Total	0.81 (0.53,0.93)	-0.90 (-0.96,-0.72)
	Male	0.78 (0.46,0.92)	-0.92 (-0.97,-0.79)
	Female	0.83 (0.56,0.94)	-0.88 (-0.96,-0.68)

CI, Confidence Interval.

a The age group for which the living conditions of a cohort were measured. E.g. for age group 0-4 years, we measured the IMR and GDP of the period that the majority of the birth cohort was 0-4 years old.

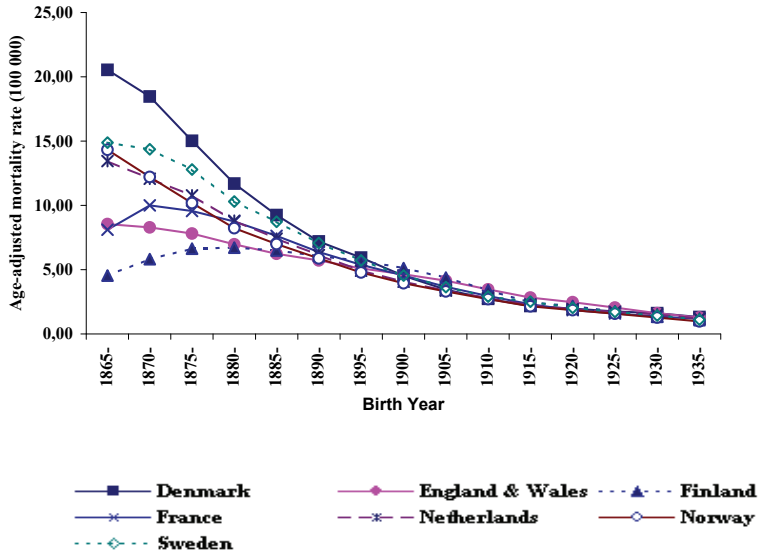

Fig. 3.1-Trends in stomach cancer mortality for five-year cohorts born between 1865 and 1939 followed for mortality in 1950-1999 in seven European countries

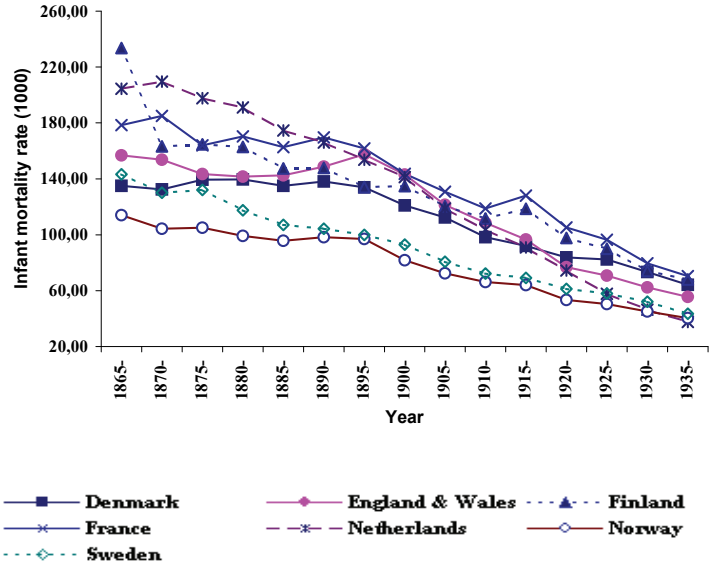

Fig. 3.2-Trends in infant mortality rate between 1865 and 1939 in seven European countries

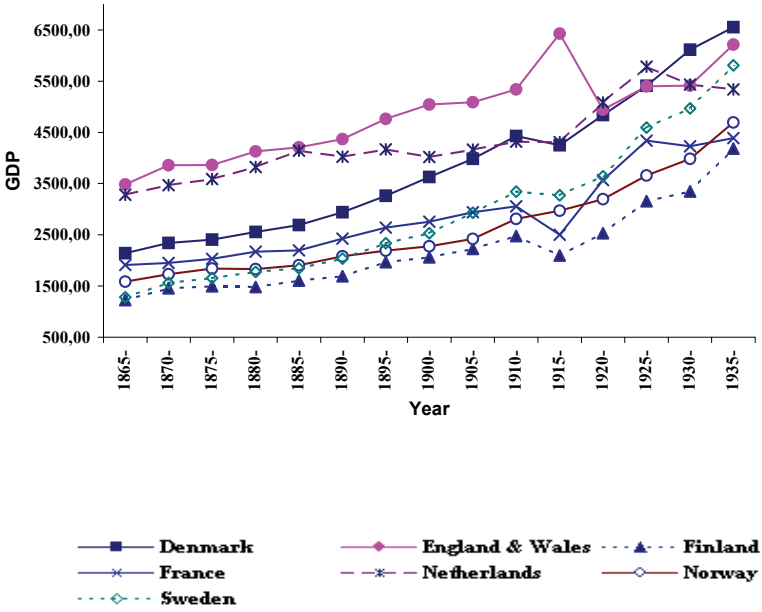

Fig. 3.3-Trends in real GDP per capita at 1995 US Dollars (adjusted by means of the purchasing power parities of 1995) between 1865 and 1939 in seven European countries

Conflict of interest statement

None declared.

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Part II:

The future mortality trends

4

Amiri M, Kunst AE and Janssen F. *The decline in ischemic heart disease mortality in seven European countries: exploration of future trends* (Submitted).

The decline in ischemic heart disease mortality in seven European countries: exploration of future trends

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Abstract

Aims: To assess the implication of a possible continuation of the decline in ischemic heart disease (IHD) mortality in future.

Methods and Results: Annual rates of decline in IHD mortality from 1980 to 2005 were determined for Netherlands, United Kingdom, France, and four Nordic countries based on regression analysis. Cause-elimination life tables were used to determine the impact of IHD on life expectancy at birth. The rates were extrapolated until 2030. In all countries, IHD mortality rates among both sexes declined incessantly until 2005. Age-adjusted mortality rates would have declined by about 50 percent in 2030 as compared to 2005 if past trends were to continue. The impact of IHD on life expectancy at birth would decline by about 25 to 50 percent in most populations. The absolute numbers of IHD deaths would decline slowly or even increase in some countries, because of population ageing.

Conclusions: If current IHD mortality trends would continue, IHD would lose much of its importance as a cause of premature death in the near future. As the incidence and disabling impact of IHD might decline to a much lesser extent, prevention of IHD related disability instead of mortality may become increasingly important in the future.

Key Words: Ischemic heart disease, mortality trend, Europe, projections, absolute number of death, potential life-years-gained.

4.1. Introduction

Although mortality from IHD had fallen substantially in the past decades, it remains the leading cause of death in Europe [1]. Previous studies have confirmed this remarkable steady and substantial decline of mortality in western Europe over recent decades [2-4], especially the past 30 years [5], with greater decreases in some than in other countries [6]. Causes of the decline are complex but changes in diet appear to play a major role; the more recent declines in western Europe also reflect improvements in modern cardiovascular treatment [5]. The decline in IHD mortality, however, does not necessarily mean a decline in IHD deaths. The absolute number of IHD deaths might continue to increase due to ageing of European population [7-9].

The main aim of this study is to assess the implication of a possible continuation of the decline in mortality from IHD in the future. Assuming a continuation of recent trends, we will assess what would be the rates of IHD mortality and its impact on life expectancy on men and women in seven European countries up to 2030. We also aim to explore whether a reduction in IHD mortality rates would offset the effects of population ageing on the future number of deaths from IHD. In addition, we aim to assess whether IHD mortality trends would be converging or diverging among European populations if recent trends in IHD mortality in these countries were to continue in the next 25 years.

It should be emphasized that our study is not a prediction of future trends, but an exploration of possible future trends based on the extrapolation of past trends. This extrapolation provides a baseline scenario for scenario studies that, by using disease-specific population models, might aim to evaluate the specific impact of future changes in the prevalence of one or more IHD risk factors (e.g. smoking, obesity, hypertension) or in the treatment of IHD patients.

4.2. Materials and Methods

Data for Denmark, Finland, France metropolitan, the Netherlands, Norway, Sweden and the United Kingdom on the number of deaths from IHD (ICD codes 410-414 for ICD-8 and ICD-9, I20-I25 for ICD-10 [10, 11]) and corresponding numbers of population at risk, by sex and five-year age groups for the years 1980 to 2005 have been obtained from Eurostat (Denmark from 1999-2001, France from 1998-2005, and other countries from 2000 to 2005) and national data sources (1980-1999) [12]. The historical national data for England & Wales and France were transformed into data for United Kingdom and France metropolitan, by applying age and sex-specific correction factors, based on the comparison of IHD mortality rates in 1995.

To describe trends in IHD mortality between 1980 and 2005, sex-specific age-standardized mortality rates were calculated using direct standardization, taking the total EU25 population by five year age group in 2005 as the standard

population (source: Eurostat website). In addition, we estimated sex- and country- specific annual mortality changes (%) over the period 1980-2005 by means of age-period log-linear regression analysis. The dependent variable was the number of deaths, with the person-years at risk (estimated by the midyear population) as offset variable. We used age by five year age groups (from 0 to 80+) (categorical) and single calendar year (continuous) as independent variables. Annual mortality changes (%) were calculated by this formula: *100*(exp (b)-1*), in which *b* is the parameter estimate of the calendar year variable.

To project age, sex, and country-specific mortality rates for the years 2010, 2015, 2020, 2025, and 2030, we applied the estimated annual changes (%) in mortality in the period 1980-2005 for all age groups combined to average national age-specific mortality rates in 2000-2005 (average year used as t_0). The formula we used (country and sex-specific): ${}_nM_x^{t_0+t} = {}_nM_x^{t_0} \bullet ({}_nc_x^* + 1)^t$. Where c^* is the annual decline (*exp(b)-1*) for all age groups multiplied by a ratio expressing the annual decline in the age groups 40-59, 60-79, and 80+ relative to the annual decline for all age groups (unweighted average over all countries).

We thus assumed that the mortality trends in the past 25 years (from 1980 to 2005) would continue for the coming 25 years, thereby taking into account age differences in the mortality decline.

Future IHD mortality numbers were estimated by applying the future sex and age-specific rates to the projected sex and age-specific population sizes for the different countries up to 2030. These future population numbers have been obtained from Eurostat (baseline variant), except for Norway for which the data have been obtained from Statistics Norway (medium national Growth variant) (http://statbank.ssb.no/statistikkbanken).

The impact on life expectancy is assessed by means of the potential gained in life expectancy (PGLE) due to IHD. For the years 2005 and 2030, we prepared cause-elimination life tables using projected all-cause mortality rates and projected IHD mortality rates for each respective projection year. All-cause mortality rates –obtained from the Human Mortality Database (HMD)- were projected using the same procedures as for IHD.

4.3. Results

Figure 4.1 shows changes in mortality rates from IHD in seven European countries according to year of death from 1980 to 2005. In all seven European countries, IHD mortality rates declined for both men and women. In each country, relative declines were slightly larger for men (inter-country range -2.70 to -4.17) than for women (range -1.89 to -3.67). Relatively strong declines were observed in the Netherlands, Sweden and Denmark. The rank order of decline in countries remained about similar over time for both sexes. The decline persisted until 2005, with no consistent evidence for a deceleration.

Table 4.1 summarizes the projected IHD mortality rates and potential gained in life expectancy (PGLE) for IHD in seven European countries in 2030. In all seven European countries, age-adjusted mortality rates would have substantially declined in 2030 compared to 2005 if past trends were to continue. For most populations, the rate ratios comparing 2030 to 2005 are close to 0.50, indicating an about 50 percent decline in mortality rates if past trends were to continue. Declines larger than 50 percent are projected for men and women in Denmark, Sweden, and the Netherlands, and for men in the United Kingdom.

Although the seven European countries differ in the pattern of decline over time, they would show some convergence in IHD mortality rates until 2030. For example, the low French mortality levels of 2005 would be reached by the Dutch and the Danish in 2030. Because mortality rates of men showed slightly stronger declines than rate of women in all countries, there would be a convergence in mortality from IHD among men and women in most countries.

The projected PGLE will decrease in 2030 for both men and women in all countries. The declines in PGLE are generally smaller than those for age-adjusted mortality rates, because estimates for PGLE are positively influenced by the higher levels of total life expectancy in 2030 (due to decreasing levels of total mortality). Among men, the PGLE would decline between 2005 and 2030 by 25 to 50 percent in most countries, with a smaller (10 percent) declines in France. About similar declines are projected for women, although with greater variability between countries.

Figure 4.2 shows the projected absolute number of deaths from IHD for men and women from 2005 until 2030. In all seven countries, absolute number of IHD deaths will not substantially decrease, and in some cases even increase, because of the ageing of European populations. An increase in absolute numbers of IHD deaths is expected to occur especially after 2020, when the post-war Baby Boom cohort will enter old age.

Table 4.1– Age standardized IHD mortality rates (per 100 000) and potential gained in life expectancy (PGLE), projections in seven European countries by sex from 2005 to 2030

	Year	**Country**						
		Denmark	United Kingdom	Finland	France	Netherlands	Norway	Sweden
Men								
Mortality	2005	209.25	267.40	313.07	93.64	133.74	182.20	230.93
rates	2030	90.13	120.22	163.25	55.55	61.43	102.74	104.70
Ratio	2030/2005*	0.43	0.45	0.52	0.59	0.46	0.56	0.45
PGLE	2005	1.97	3.31	3.98	1.17	1.38	2.12	2.85
	2030	1.01	2.23	3.03	1.05	0.76	1.60	1.86
Ratio	2030/2005	0.51	0.67	0.76	0.90	0.55	0.75	0.65
Women								
Mortality	2005	119.51	146.00	171.96	42.38	65.38	92.42	121.31
rates	2030	52.52	69.76	121.52	26.36	31.22	61.91	55.44
Ratio	2030/2005	0.44	0.48	0.71	0.62	0.48	0.67	0.46
PGLE	2005	1.76	2.35	4.10	0.98	1.05	1.79	2.34
	2030	0.77	1.44	3.62	0.84	0.49	1.42	1.29
Ratio	2030/2005	0.44	0.61	0.88	0.86	0.47	0.79	0.55

* The figure of 2030 divided by the related figure in 2005.

For Denmark, the values for 2005 are not observed but projected.

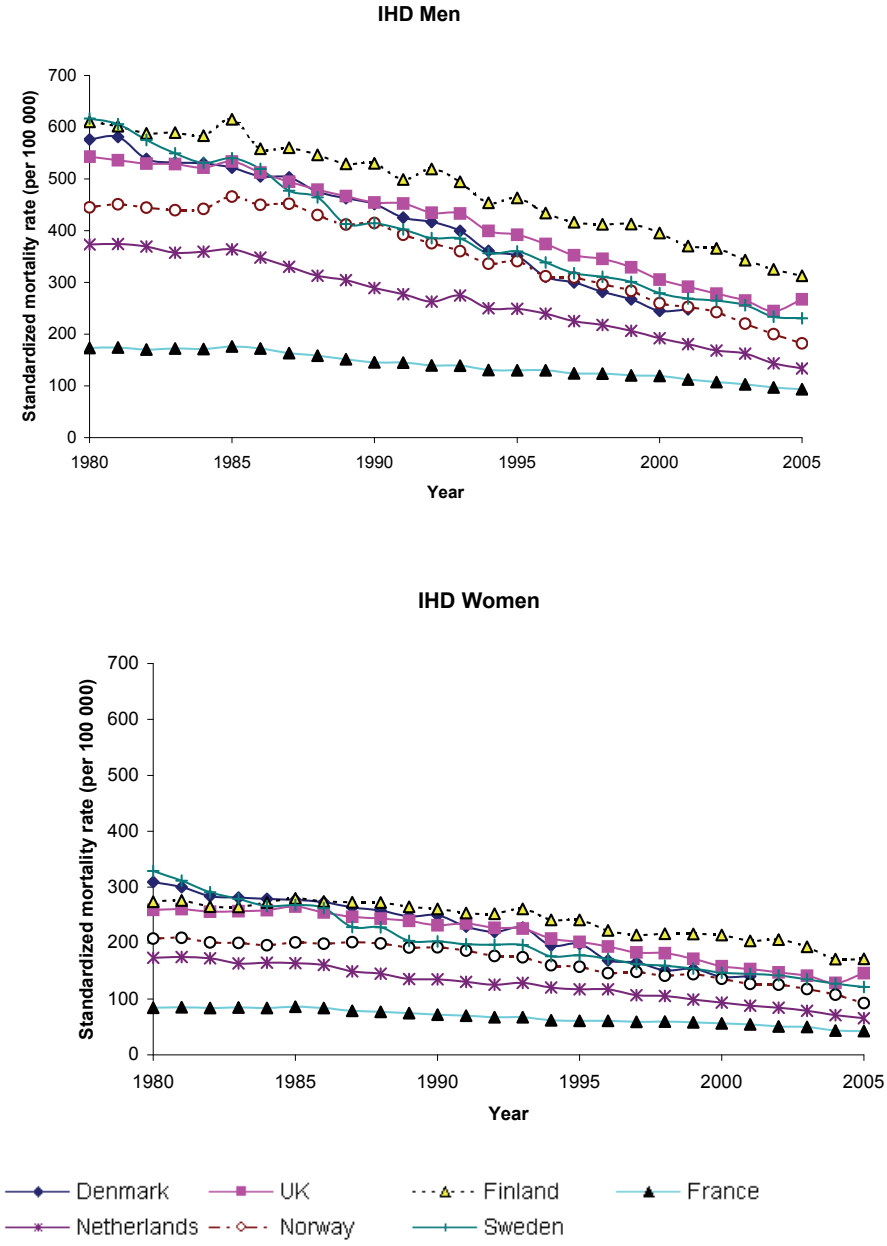

Figure 4.1- Age-standardized IHD mortality rates (per 100000) in seven European countries by sex: 1980-2005 [*] [$]

$. Data for Denmark until 2001. *. Corresponding estimates of annual mortality changes (%) for men (women) are for Denmark -4.17(-3.67), United Kingdom -3.40(-2.72), Finland -3.30 (-1.89), for France -2.70(-2.57), the Netherlands -4.11(-3.53), Norway -3.46 (-2.56), and Sweden -3.97(-3.64).

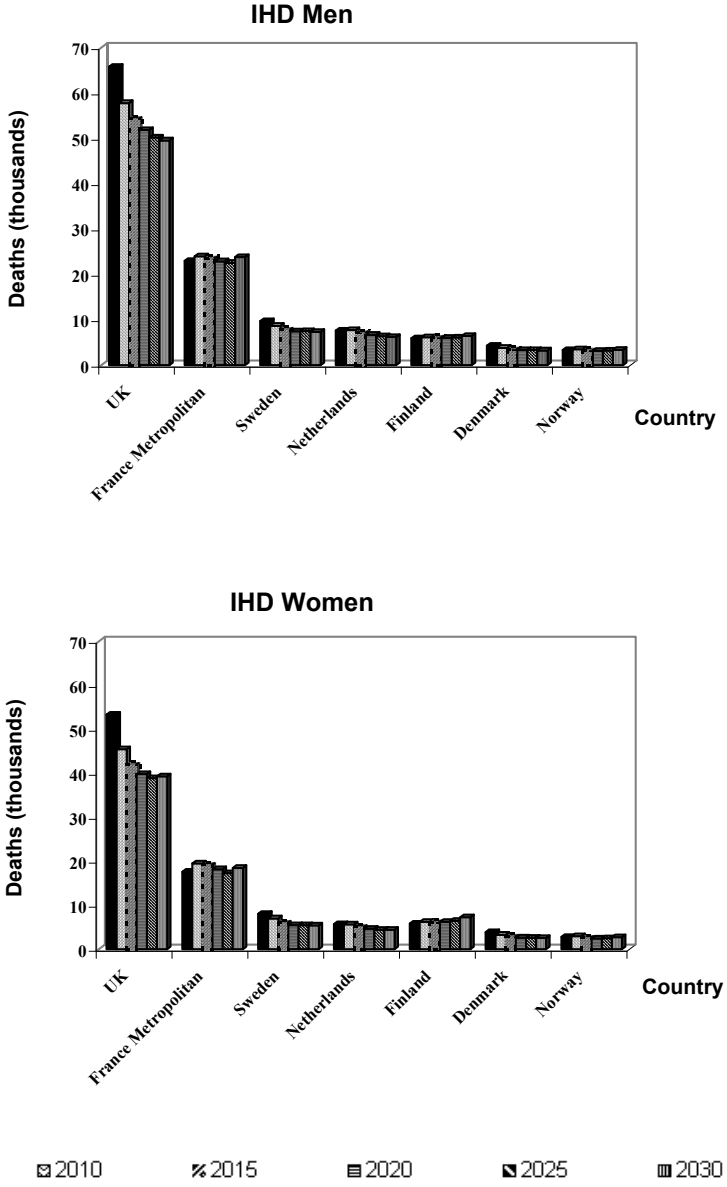

Figure 4.2- Absolute number of deaths (thousands) from IHD in seven European countries, by country and sex: 2005-2030

For Denmark, the values for 2005 are not observed but projected.

4.4. Discussion

The dramatic and persistent decline in IHD mortality observed for the 1980s and 1990s was found to continue at an undiminished pace until 2005 in each of the seven European countries included in this study. If this decline were to continue, IHD mortality rates would reach unprecedented low levels. In most populations, age-adjusted mortality rates would have declined by about 50 percent in 2030 as compared to 2005.

While IHD mortality rates have halved over recent decades, because of population ageing, the total numbers of deaths have not declined correspondingly. Our projections showed that numbers of deaths are likely to remain constant or even increase in some European populations, especially after the year 2020, when the Baby Boom generation will reach old age. The future burden of IHD mortality will increasingly affect older groups, who thus may stretch health care systems [13].

This contrast between declining age-specific mortality rates and constant absolute numbers of deaths raises question on how to evaluate the importance of IHD as a cause of death. In any generation, people will have to die anyhow. The main issue is therefore not whether people will die, but until what age they can expect to live. Similarly, the importance of IHD as a cause of death should not only be measured by the number of people dying from this disease, but also by taking into account the number of years of life that they lose due to death from IHD. We observed that the effect of IHD on life expectancy would decline by about 25 to 50 percent in most populations. IHD mortality rates would decline especially at younger ages, thus transforming IHD increasing more into an old-age disease with a limited impact on life expectancy at birth.

Although the extrapolation of past trends is not the only means of making projections, explorations of the future should also be fairly realistically based on trends observed in the past. Extrapolation-based projections provides a basis for more specific scenario studies that would focus on the effect of specific risk factors or health care [14]. The trends that we projected may provide a new perspective to appreciate the future implications of currently observed trends, and the likely impact of new epidemiological trends and health care policies.

The three main potential explanations for the recent reduction in IHD mortality are the primary prevention in the general population, interventions that reduce the case fatality rate from acute events, and secondary prevention to prolong life in patients with diagnosed disease [15]. Lifestyle factors affecting past IHD mortality trends include cigarette smoking, dietary habits (e.g. energy intake, consumption of fruit and vegetables), and physical activity [16]. Attributing past falls in IHD mortality to risk factor changes or effective medical interventions is difficult because favorable trends in both have occurred simultaneously. The relative contributions may vary widely from country to country, and from time to time [17]. Evidence is accumulating that the early

declines in IHD mortality are, to a large extent, due to changes in diet and other lifestyle factors whereas the more recent declines are also due to improvements in modern cardiovascular treatment [5].

Only time will tell whether these factors will together ensure a similar pace of decline in IHD mortality until 2030. Future declines in IHD mortality would be expected to follow from the introduction of new treatments and increased uptake of existing treatments, both in the treatment for acute IHD and in the long term care for IHD survivors. However, medical treatment may reach limits especially among the oldest old, because of persisting problems such as high levels of co-morbidity. Limitations to efficacious live-saving treatment of older IHD patients is reflected by much slower rates of decline of IHD mortality among 80 years old since 1980, which were taking into account in our projections until 2030.

Further improvement with regards to life style might occur thanks to growing awareness on the importance of relevant behaviors among more well-informed and better educated populations of the future. This may stimulate for example further declines in smoking prevalence, which is likely to be backed up by far-reaching tobacco control policies. On the other hand, other risk factors may become more important, such as diabetes mellitus (DM) [18, 19]. The envisaged effect on IHD mortality may however be counteracted by efficacious medical treatment of diabetic people, thus reducing case fatality rates. Evidence from clinical trials for example support the value of lipid-lowering therapy for patients with DM [20].

The increasing prevalence of DM is driven largely by increasing prevalence rates of obesity and overweight [22, 24-26], with its increased risk of death from IHD [20]. Obesity prevalence is expected to further increase in the in the near future [21, 22]. In further calculations, we therefore estimated what would happen to future IHD mortality trends if (a) recent trends in average body mass index (BMI) levels in western Europe would continue between 2005 and 2030 and (b) the relationship between BMI and IHD mortality as observed in recent studies would also persist in the future. We found that the effect would be to increase IHD mortality by about 10 percent between 2005 and 2030. This increase is important, but relatively small as compared to the 50 percent declines in IHD mortality rates that we projected based on trends in IHD mortality in the past 25 years.

The decline in IHD mortality in the future is unlikely to be paralleled by a similar decline in IHD incidence, especially when incidence rates will be affected by the obesity epidemic. Declining case-fatality rates, thanks to improved treatment of IHD patients, are likely to make substantial contribution to falling mortality rates. As a result, while IHD mortality is likely to decline, especially at younger ages, the age-specific prevalence of IHD among elderly populations may increase.

The observed sharp decline in mortality might lead one to expect a decrease in health care utilization. In reality, however, health care providers are facing increases in demand [23]. As with the trends in absolute number of IHD deaths, part of this increase in hospitalizations will be prompted by the ageing of Baby Boomers [24]. Generally, the ageing of the population and the demographic changes projected for 2030 will have a major impact on the prevalence of and cost of care for IHD [25], with different slopes between populations [26].

In conclusion, if current IHD mortality trends would continue, IHD mortality would lose much of its importance in the future and become mainly a death related to old age. On the other hand, the prevalence of IHD is likely to increase, and so is the related demand for health care. The priority of prevention and treatment of IHD therefore will have to be shifted from prevention of death to prevention of disability.

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Kunst AE, **Amiri M**, Bonsel GJ and Janssen F. *The decline in stroke mortality. Exploration of future trends in seven Western European countries* (Submitted).

The decline in stroke mortality. Exploration of future trends in seven Western European countries

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Abstract

Background and objectives: If the secular decline in stroke mortality is to continue in the near future, the importance of stroke mortality would reduce to some unknown extent. This paper aims to make projections of future trends in stroke mortality in the year 2030 based on recent trends in stroke mortality in seven Western European countries.

Methods: Annual rates of decline in stroke mortality from 1980 to 2005 were determined for men and women in United Kingdom, France, Netherlands and four Nordic countries on the basis of regression analysis. Estimated rates of decline were extrapolated until 2030. Cause-elimination life tables were used to determine the effect stroke in 2030 in terms of potential years of life lost (PYLL). The absolute numbers of stroke deaths in 2030 were estimated using national population projections of Eurostat.

Results: In all countries, stroke mortality rates declined incessantly until 2005 among both men and women. If these trends were to continue, age-adjusted mortality rates would decline by about one half between 2005 and 2030, with larger declines in France (about two thirds), and smaller declines in the Netherlands, Denmark and Sweden (about one quarter). Similar rates of decline would be observed in terms of PYLL. Because of population ageing, the absolute number of stroke deaths would decline slowly in United Kingdom and France, and stabilize or even increase in other countries.

Conclusions: In the near future, stroke may lose much of its importance as a cause of premature death, but remain a frequent cause of death among elderly populations. For these populations, the prevention of stroke-related disability instead of mortality may become increasingly more important.

Key Words: Stroke, mortality, secular trends, future, projections

5.1. Introduction

Stroke mortality has strongly declined during the 20th century. Studies from Western Europe [1-3], Northern America [4], Australia [5] and New Zealand [6] consistently showed that mortality from stroke declined until the most recent years of observation. International reviews showed that this mortality decline is paralleled by declines in both incidence rates and case-fatality rates [7]. Whereas declining incidence rates are likely to reflect improvements in life styles and environmental exposures in different phases of life, declining case-fatality rates also reflect ongoing progress in secondary prevention and treatment of stroke.

The strong declines in the past raise important questions about the future of stroke mortality. A possible continuation of these declines may or may not imply that stroke would cease to become an important cause of premature death, and that its effect of life expectancy would become marginal too. Further, the rapid ageing of European populations in the next decades may or may not compensate for this mortality decline. If it were, the number of elderly people dying from stroke would increase rather decrease in the next decades.

To our knowledge, only a few international publications have reported on projections of future trends in stroke mortality [8]. In addition, some of the projections are based on stroke mortality trends in the 1980s or early 1990s [9], and therefore could not take into account trends in stroke mortality since the mid 1990s. Taking into account recent trends can however change future perspectives. For example, stroke mortality decline was reported to stagnate in the early 1990s in some countries, including the USA, but a reinforcement of stroke mortality decline was observed afterwards. In order to create a stable empirical basis for projections of future trends, and avoid dependency on short-term irregularities, it is important to consider stroke mortality trends over long span of years [10]. Similarly, the empirical basis for future projections could be expanded by also considering trends in countries with similar levels of socioeconomic development.

The aim of this paper is to present projections of future trends in stroke mortality in seven Western European countries until 2030. Future trends will be projected on the basis of a careful assessment of past trends among men and women in seven countries. Based on this assessment, projections are made of future trends in stroke mortality. Two complementary measures will be used to express the importance of stroke mortality: the potential years of life lost (PYLL), and the absolute number of deaths with stroke as the underlying cause. The PYLL aims to express the importance of future level of stroke mortality rate as a cause of premature death, through its effect on life expectancy at birth. Compared to this measure, projections the absolute number of deaths also takes into account the rapid ageing of the European populations in the next decades.

5.2. Materials and Methods:

Data for Denmark, Finland, France metropolitan (i.e. mainland France), the Netherlands, Norway, Sweden and England and Wales on the number of deaths from stroke (ICD codes 430-434 and 436-438 for ICD-8 and ICD-9, and I60-I69 for ICD-10 [11, 12]) by sex and five-year age groups for the years 1980 to 2005 have been obtained from national data sources (1980-1999) and from Eurostat (Denmark from 1999-2001, France from 1998-2005, and other countries from 2000 to 2005) [13]. Corresponding numbers of population at risk were obtained from similar sources. As the study period included different revisions of the WHO International Classification of Diseases (ICD), we adjusted for effects of coding changes using a regression-based method that is reported elsewhere [11, 12]. The historical national data for England and Wales and France were transformed into data for United Kingdom and France metropolitan, by applying age and sex-specific correction factors, based on the comparison of stroke mortality rates in 1995.

To describe trends in stroke mortality between 1980 and 2005, sex-specific age-standardized mortality rates were calculated using direct standardization, taking the average national male and female populations by five year age groups over 2000-2005 (2000-2001 for Denmark) as the standard populations. In addition, we estimated sex- and country-specific annual mortality changes (%) over the period 1980-2005 by means of log-linear regression analysis. The dependent variable was the number of deaths, with the person-years at risk (estimated by the midyear population) as offset variable. The regression model included five-year age groups (from 0 to 80+) as a categorical variable, and single calendar year as a continuous variable. Annual mortality changes (%) were calculated as *100*(exp (b)-1*), in which *b* is the regression coefficient to the calendar year variable.

To project age-specific mortality rates until 2030, we assumed that the mortality trends from 1980 to 2005 would continue for the next 25 years. We therefore applied the estimates of the annual rate of change in mortality in the period 1980-2005 to the national age-specific mortality rates in 2005. This projection was made for each sex and county separately. The projection formula was:

$${}_nM_x^{t_0+t} = {}_nM_x^{t_0} \bullet ({}_nc_x^* + 1)^t$$, where

${}_nM_x$ is mortality rate in the age interval x, x+n;
t_0 is the baseline year 2005;
t is the length of the projection period, with 2006=1 and 2030=25 years;
c^* is the annual rate of mortality change observed over the period 1980-2005.

In general, past mortality declines were larger in younger age groups. In order to take this age effect into account, the factor c^* above was estimated for the age groups 40-59, 60-79 and 80+ years separately. For this, the c^* value for all age groups combined was multiplied by three ratios expressing the annual decline in, respectively, the age groups 40-59, 60-79, and 80+ years relative to the annual decline for all age groups. To reduce the effect of chance fluctuations, these ratios were averaged estimated across all seven countries. The resulting values for men were 1.10, 1.17, and 0.79 for the age groups 40-59, 60-79, and 80+ years, respectively. The ratios for women were 1.15, 1.41, and 0.79.

The absolute number of stroke deaths was projected by applying the projected age-specific mortality rates to the projected age-specific numbers of men and women living in the different countries up to 2030. The future population numbers of the EU member states were obtained from Eurostat, taking the baseline demographic variant. For Norway, data were obtained from Statistics Norway, taking the medium national Growth variant (http://statbank.ssb.no/statistikkbanken).

The importance of stroke mortality was expressed by means of two complementary measures. First, we expressed the impact of stroke mortality on life expectancy by means of the potential years of life lost (PYLL) measure. This measure expresses the extent to which life expectancy were to increase in case of the hypothetical elimination of stroke in the years 2005 and 2030. For 2005, we prepared cause-elimination life tables using all-cause mortality rates and stroke mortality rates observed for 2005. For 2030, we used our own projections of stroke mortality; while we also projected all-cause mortality rates for 2030 using the same methodology as used for stroke mortality.

For Denmark, stroke mortality data were available until 2001 instead of 2005. Therefore, the year 2001 was used as the end year for the analysis of past trends in stroke mortality, and the baseline year for future projections of stroke mortality. All-cause mortality rates for Denmark for 2002-2005 were however available from the Human Mortality Database (www.mortality.org).

5.3. Results:

Figure 5.1 shows changes in stroke mortality rates in seven Western European countries according to year of death from 1980 to 2005. In all seven European countries, stroke mortality rates declined among both men and women. In the United Kingdom, Norway and Finland, stroke mortality rates declined by almost 3 percent per year. Relatively strong declines were observed in France (more than 4 percent per year). Declines were smallest in Denmark and Sweden (about 1 to 1.5 percent per year) followed by the Netherlands (about 2 percent). The declines persisted until 2005. Even though each country shows irregularities in the pace of decline, there is no consistent evidence for a deceleration of the mortality decline in recent years.

Table 5.1 presents the projected age-standardized mortality rates for men and women in the seven countries in 2030. In all countries, age-adjusted mortality rates would have substantially declined in 2030 compared to 2005 if past trends were to continue. Age-adjusted mortality rates would decline by about one half between 2005 and 2030. Larger declines would occur in France; with the rate ratio of 0.33 for men indicating a two thirds decline. Smaller declines would occur in the Netherlands, Denmark and Sweden, for which the rate ratios of about 0.70 to 0.80 indicate a decline by about one quarter. In each country, mortality rates are projected to decline a bit more strongly among men than among women.

In terms of PYLL, the importance of stroke mortality would also decline to an important extent. When averaged across all countries, the PYLL estimates for men decline from 0.87 years in 2005 to 0.48 years in 2030. For women, the PYLL declines from 1.35 to 0.81 years. Thus, in 2030, the hypothetical elimination of stroke mortality would increase life expectancy at birth by about 0.5 years for men, and 0.8 years for women. This effect has an about similar magnitude in most countries. A PYLL close to one year would be observed only among Swedish and Danish women. Much smaller estimates are projected for France only (0.23 years for men and 0.41 years for women).

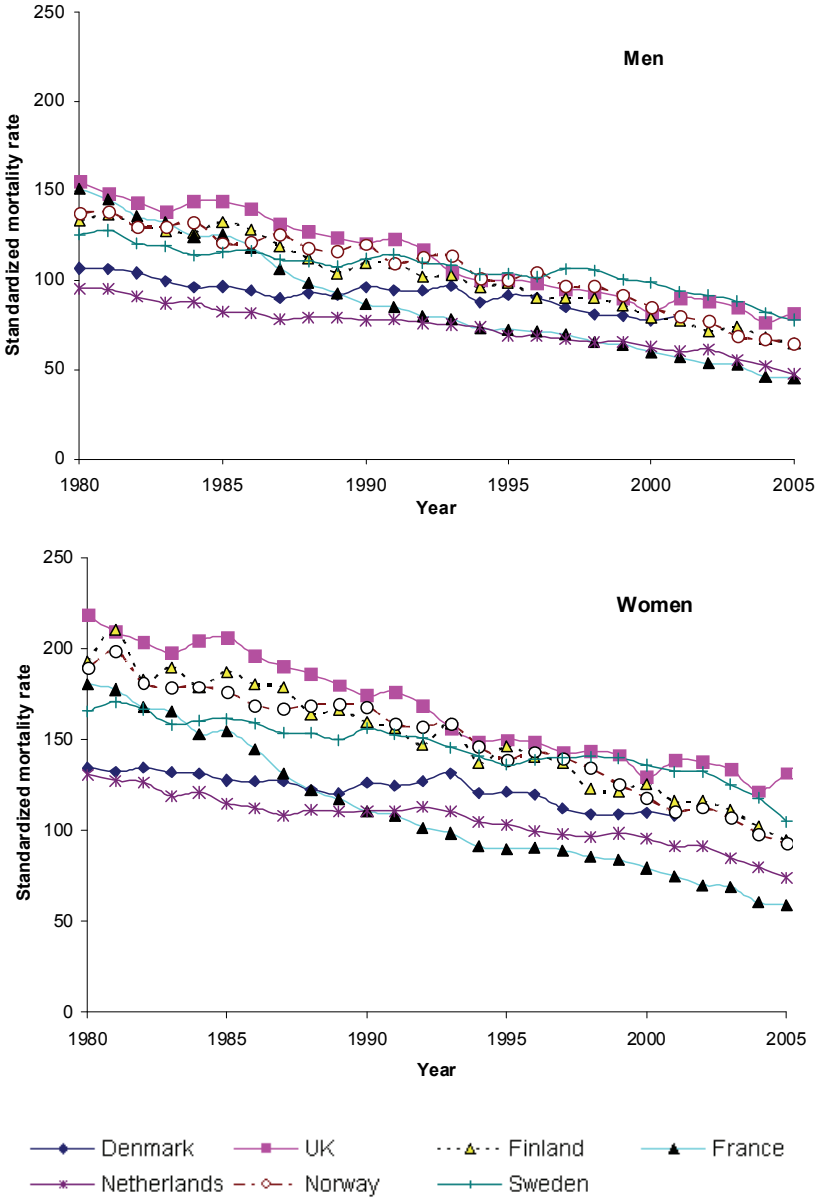
Figure 5.2 shows the projected absolute number of stroke deaths from 2005 until 2030. The rate of change strongly varies between countries and over time. The absolute number of stroke deaths is projected to decline in the United Kingdom and in France in the first 15 or 20 decades. In both countries, this decline would however stagnate and even reverse after 2020, when the post-war Baby Boom cohort will enter old age (70 years and over). In Netherlands, Sweden and Denmark, increases in the absolute number of stroke deaths are projected to occur over the entire period, but especially after 2020. Relative stable numbers of deaths are projected for Norway and Finland.

Table 5.1. Age standardized stroke mortality rates and potential years of life lost (PYLL) observed in 2005 and projected for 2030. Men and women in seven European countries.

Sex Index	Year *	Country						
		Denmark	United Kingdom	Finland	France	Nether-lands	Norway	Sweden
Men								
Mortality rate (per 100,000)	2005	74.38	81.33	64.72	45.40	47.34	64.45	77.81
	2030	54.63	39.00	32.27	15.03	30.61	35.87	59.36
	2030/2005	0.73	0.48	0.50	0.33	0.65	0.56	0.76
PYLL (in years)	2005	0.87	1.10	0.98	0.70	0.69	0.84	0.88
	2030	0.63	0.51	0.48	0.23	0.43	0.45	0.65
	2030/2005	0.72	0.46	0.49	0.32	0.63	0.53	0.74
Women								
Mortality rate (per 100,000)	2005	104.40	131.57	94.51	58.78	73.99	92.73	105.02
	2030	81.84	71.96	52.75	22.65	53.89	54.24	86.27
	2030/2005	0.78	0.55	0.56	0.39	0.73	0.58	0.82
PYLL (in years)	2005	1.27	1.69	1.56	1.10	1.16	1.35	1.30
	2030	0.97	0.85	0.83	0.41	0.82	0.74	1.04
	2030/2005	0.76	0.50	0.53	0.37	0.71	0.55	0.80

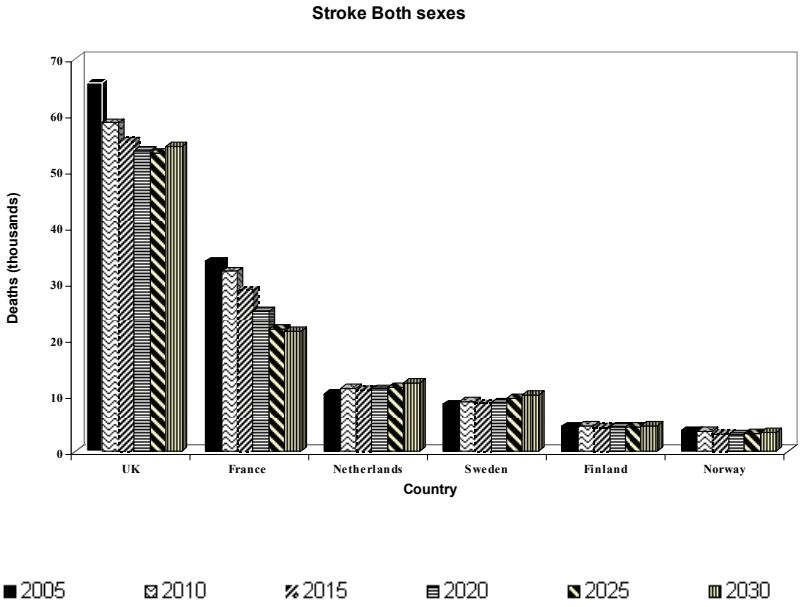
* 2030/2005 = value for 2030 as ratio to value for 2005.

Figure 5.1. Trend between 1980 and 2005 in age-standardized stroke mortality rates (per 100,000 person years). Men and women in seven European countries *



* Corresponding estimates of percent annual decline for men (women) are for: Denmark -1.26 (-1.01), United Kingdom -2.89 (-2.34), Finland -2.91 (-2.81), France -4.66 (-4.35), Netherlands -2.25 (-1.78), Norway -2.76 (-2.68), Sweden -1.54 (-1.46).

Figure 5.2. Projected trends between 2005 and 2030 in the absolute number of stroke deaths (men and women combined) in seven European countries



5.4. Discussion

Summary

We observed a strong decline in stroke mortality in the past decades, both among men and women, in each of the seven countries studied. If these trends were to continue in the future, stroke mortality rates in 2030 would be substantially lower than they were in 2005. Similarly, strong declines would be observed in the effect of stroke on life expectancy. In 2030, the effect of stroke on life expectancy would be less than 1 year in nearly all female populations, and about 0.5 years in most male populations.

Despite this decline in stroke mortality risk, the absolute number of deaths from stroke will not substantially decline, and even increase at the shorter and longer term. This increase is due to the ageing of the national populations, especially after the year 2020, when the Baby Boom generations will reach old age. Though, less important as a cause of premature death, stroke remains a common cause of death in Western Europe's ageing populations.

Data limitations

An important potential problem relates to the coding of underlying causes of death in national published data. Problems related to changes in revisions of the ICD have been evaluated by our team and taken into account where necessary [11, 12]. Changes over time in certification practices by physicians are another area of concern, although they are unlikely to explain the observed decline in stroke mortality [14]. Moreover, similar rates of mortality decline have been observed in epidemiological studies with standardized ascertainment of stroke cases within registration areas [15].

Our results for seven Western European countries cannot be generalized to other regions of the world. Recent trends in stroke mortality in Eastern European countries strongly differed from those in the West [16], implying that the East may differ also with regards to future trends in stroke mortality. Similarly, trends in stroke incidence and case-fatality in low income countries were found to strongly differ from the trends in high income countries [7, 17]. On the other hand, in the USA, stroke mortality has declined over recent decades with about 0.3-2.9 percent per year [18], suggesting similar trends as in Western Europe with about 0.43-4.11 [13] and 2.3 [14] percent per year.

Evaluation of projection method

Two acknowledged demographers, Wilmoth [10] and Oepen and Vaupel [19], argue that future trends in mortality can best depart from extrapolations of past trends in mortality as observed over a longer period. We therefore based our projections on the declines in stroke mortality as observed in the seven European countries over a 25 years period. The precise rate of mortality decline strongly varied between countries, as it did between subsequent decades. This variability warns us that it is difficult to accurately predict future mortality trends for specific countries during specific decades. Rather than on time-period specific projections, we concentrated on longer-term projections and similarities in these projections across the seven countries. The generalized decline in stroke mortality projected for all seven countries basically reflects the substantial and persistent decline in stroke mortality found among both sexes and all countries in the past 25 years.

As our projection model concentrates on stroke mortality, it does not take into account stroke incidence or case-fatality, nor does it model the 'driving' role of risk factors such as smoking and hypertension. The great advantage of the mortality data, as compared to stroke incidence or case fatality data, is that mortality data cover long periods of time for a large number of countries. Even though cross-national comparability of data is suboptimal, international overviews of stroke trends can be made with mortality data but not with incidence data [8]. Models based on stroke incidence and case fatality have much

higher requirements to the available empirical input, especially if the disease process is to be modelled in some detail. Our mortality projections provided in this paper can be used as the baseline or yardstick against which to check the outcomes of more sophisticated projection models for individual countries.

Interpretation

The strong decline in stroke mortality in past decades is likely to be attributable to declines in both case-fatality rates and in incidence rates. For case-fatality rates, there is consistent evidence from a large number of epidemiological studies for a steady improvement in survival rates of stroke patients. From an analysis of the complete data of the MONICA study, it was estimated that the stroke mortality decline was attributable for about two thirds to declining case-fatality rates, with declining incidence explaining the rest [20]. However, as this study is limited to individuals 35-64 years, it is uncertain whether this high estimate is representative for the older ages where most stroke deaths occur.

With regards to stroke incidence, the evidence is less consistent, as several studies reported no decrease over time in incidence rates. However, a systematic review of all available evidence concluded that stroke incidence substantially declined between the 1970's and the 2000's in high income countries [7]. The potentially large contribution of stroke incidence to stroke mortality trends is suggested by the fact that variations in stroke mortality trends between high income and low income countries, and between Eastern and Western Europe, are paralleled by similar variations in trends in the incidence of stroke. Further support comes from the finding that key risk factors for stroke incidence (e.g. smoking, hypertension, and raised serum cholesterol) could explain at least one half of the secular decline in stroke mortality in some countries.

In view of the past experiences, future reductions in stroke mortality are likely to be contingent on declines in both incidence and case-fatality rates. With regards to stroke incidence, further declines may follow reductions in the prevalence of risk factors such as smoking, hypertension, and cholesterol. New vigorous tobacco control policies in Western Europe since the 1990s are likely to decrease tobacco exposure rates of generations that will reach old age in the mid 21st century. Moreover, improvement in environmental and socioeconomic determinants, such as the rising educational levels of generations born in the 20th century, may contribute to continued declines in stroke incidence in the 21st century. Further evidence to expect such a continued decline comes from a cohort analysis that we performed of the same mortality data, and from which we concluded that the mortality declines persisted until the youngest generations, possibly due to improved environmental conditions in early life [13].

Declines in stroke incidence may however be halted by increasing prevalence of some other risk factors, notably excess weight [21]. We estimated what the potential effect on future stroke mortality levels assuming (a) that recent

trends in increasing average body mass index (BMI) levels in Western Europe would continue between 2005 and 2030 and (b) the relationship between BMI and stroke mortality as observed in recent studies would also persist in the future. We found that stroke mortality in 2030 would be 10 percent higher as compared to the situation of no increase in BMI. This increase is important, but relatively small as compared to the about 50 percent decline in stroke mortality rates that we projected for most of the seven countries.

With regards to case-fatality of stroke, future declines depend on continued progress in treatment of stroke patients. Starting treatment immediately is an important opportunity posing logistic challenges, but it may save lives and reduce the likelihood of disabilities. We expect the optimal level of drug treatment yet to arrive, including the application of *additional* drugs to *dissolve* clots (like TPA), to *slow* the degeneration of the nerve cells (like Sipatrigine and Chlormethiazole), and to *replace* brain cells damaged by a previous stroke (like Stem Cells). Intensified secondary prevention as with myocardial infarction may further decrease long term case-fatality rate of first-stroke cases.

Implications

A main challenge to stroke prevention and treatment is to maintain the rate of decline in stroke mortality observed in the past 25 years. If these declines were to continue for the next 25 years, stroke would loose much of its importance as a cause of premature death, as it would only modestly affect the life expectancy of men and women in Western Europe in 2030.

A continued decline in stroke mortality rates would not be paralleled by a similar decline in the number of people dying from stroke. Due to ageing of the population, the absolute number of stroke deaths would remain at approximately the same level. Moreover, the average age of death of stroke patients will unavoidably increase. Thus, the absolute number of elderly patients in need of intensive or terminal treatment is unlikely to diminish in the next decades.

To the extent that declines in mortality are achieved by improved survival, the future number of stroke patients would increase at a larger rate that the number of stroke deaths. This would imply that the future burden of stroke will gradually shift from a (more or less constant) mortality burden towards a (rising) morbidity burden. To respond to this shift, the treatment of stroke patients may need to give increasingly more emphasis to avoid disability and discomfort, rather than only averting death.

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Amiri M, Kunst AE and Janssen F. *The decline in stomach cancer mortality: exploration for the future in Europe* (Submitted).

The decline in stomach cancer mortality: exploration of future trends in seven European countries

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Abstract

Mortality from stomach cancer has fallen steadily during the past decades. The aim of this paper is to assess the implication of a possible continuation of the decline in stomach cancer mortality until the year 2030. Annual rates of decline in stomach cancer mortality from 1980 to 2005 were determined for the Netherlands, United Kingdom, France, and four Nordic countries on the basis of regression analysis. Mortality rates were extrapolated until 2030, assuming the same rate of decline as in the past. The absolute numbers of deaths were projected taking into account data on the ageing of national populations. Cause-elimination life tables were used to determine the importance of stomach cancer in terms of potential gained in life expectancy (PGLE). Stomach cancer mortality rates declined between 1980 and 2005 at about the same rate (3.6-4.9 percent per year) for both men and women in all countries. The rate of decline did not level off in recent years, and it was not smaller in countries with lower overall mortality rates. If this decline were to continue into the future, stomach cancer mortality rates would decline with about 66 percent between 2005 and 2030 in most populations. A two-thirds decline would also be observed in terms of PGLE, while the absolute number of stomach cancer deaths would diminish by about 50 percent. Thus, in view of the strong, stable and consistent mortality declines in recent decades, stomach cancer is likely to become increasingly less important as a cause of death in Europe in the future.

Key Words: Stomach cancer, mortality, trends, Europe, projections

6.1. Introduction

Stomach cancer is the fourth most frequent cancer [1, 2] and the world's second leading cause of cancer mortality [1]. However, it has been fallen throughout Europe during the past decades in terms of both incidence and mortality rates [3, 4], mainly as a result of remarkable improvement of living conditions in European societies [5-8]. Efforts to reduce global cancer disparities begin with an understanding of geographic patterns in cancer incidence, mortality and prevalence, by studies such as GLOBOCAN [9, 10], EUROCARE [11], and Five Continents databases [12]. Survival increased and mortality decreased through the combination of earlier detection, better access to care and improved treatment [13]. There has also been a concomitant change in lifestyle and environmental exposures over successive generations [14], including changes in exposures to risk factors in early life [15].

Several studies conducted projections of future trends in stomach cancer mortality in European countries [7,12,14-17]. Mortality rates were generally expected to decline further. Based on the cancer mortality trends in the European Union until 2000, one study projected a further fall by 11% in age-standardized cancer mortality from 2000 to 2015 [16]. A Dutch study also projected a substantial decline in stomach cancer mortality until 2015, based on trends until 2000 [17]. Similarly, an Irish study predicted mortality from stomach cancer to fall further in the near future, although at a slower rate than in the recent past [18].

European studies included projections of the absolute number of cancer deaths, thereby taking into account the rapid ageing of European populations in the forthcoming decades [14-16]. Population ageing alone may induce a strong increase in the absolute number of incident cases and deaths for many types of cancer. However, in the case of stomach cancer, this demographic effect may be offset by an opposite epidemiological effect if the recent decline in age-specific mortality rates were to continue in the future.

The aim of this study was to assess, for seven European countries, the implications of a possible continuation of the recent declines in stomach cancer rates. Future trends were evaluated not only in terms of mortality rates, but also in terms of potential years of life gained – a measure used to assess the importance of a cause of death for people's life expectancy. In addition, we assessed future trends in absolute numbers of death, thereby taking into account the ageing of national populations.

Projections of future mortality trends should be based on a careful analysis of trends in the past [19, 20]. We therefore started the analysis with a description of trends in stomach cancer mortality over a long period, from 1980 up to 2005, in order to check whether mortality declines continued undiminished until recent years. In addition, we assessed whether the rate of decline was similar for all seven countries and both sexes, despite differences in overall levels of stomach

mortality rates. We thus aimed to identify a stable and consistent long-term mortality trend that could serve as a basis for projections into the future.

6.2. Material and Methods

Data for Denmark, Finland, France metropolitan, the Netherlands, Norway, Sweden and England and Wales on the number of deaths from stomach cancer (ICD code 151 for ICD-8 and ICD-9, C16 for ICD-10 [21]) and corresponding numbers of population at risk, by sex and five-year age groups for the years 1980 to 2005 have been obtained from Eurostat (Denmark from 1999-2001, France from 1998-2005, and other countries from 2000 to 2005) and national data sources (1980-1999) [22]. The historical national data for England and Wales and France were transformed into data for United Kingdom and France metropolitan, by applying age and sex-specific correction factors, based on the comparison of stomach cancer mortality rates in 1995.

To describe trends in stomach cancer mortality between 1980 and 2005, sex-specific age-standardized mortality rates were calculated using direct standardization, taking the average national male and female populations by five year age groups over 2000-2005 (2000-2001 for Denmark) as the standard populations. In addition, we estimated sex- and country- specific annual mortality changes (%) over the period 1980-2005 by means of age-period log-linear regression analysis. The dependent variable was the number of deaths, with the person-years at risk (estimated by the midyear population) as offset variable. We used age by five year age groups (from 0 to 80+) (categorical) and single calendar year (continuous) as independent variables. Annual mortality changes (%) were calculated by this formula: *100*(exp (b)-1*), in which *b* is the parameter estimate of the calendar year variable.

The observed declines vary by age. To project age, sex, and country-specific mortality rates until 2030, we applied the estimated annual changes (%) in mortality in the period 1980-2005 for all age groups combined to average national age-specific mortality rates in 2000-2005 (average year used as t_0). The formula we used (country and sex-specific): ${}_nM_x^{t_0+t} = {}_nM_x^{t_0} \bullet ({}_nc_x^* + 1)^t$. Where c^* is the annual decline (*exp(b)-1*) for all age groups multiplied by a ratio expressing the annual decline in the age groups 40-59, 60-79, and 80+ relative to the annual decline for all age groups (unweighted average over all countries). The applied ratios that express the annual decline in age group relative to annual decline for all age groups, for men were 0.92, 1.03, and 0.99 for the age groups 40-59, 60-79, and 80 and more, respectively. The ratios for women were 0.85, 0.97, and 1.09, respectively. We thus assumed that the mortality trends in the past 25 years (from 1980 to 2005) would continue for the coming 25 years, thereby taking into account age differences in the mortality decline.

Looking into the projected mortality rates, absolute number of deaths, and potential gained in life expectancy (PGLE) in 2030, it can be measured if stomach cancer is a less important cause of death in the future.

Future stomach cancer mortality numbers were estimated by applying the future sex and age-specific rates to the projected age-specific population sizes for the different countries up to 2030. These future population numbers have been obtained from Eurostat (baseline variant), except for Norway for which the data have been obtained from Statistics Norway (medium national Growth variant) (http://statbank.ssb.no/statistikkbanken).

The impact on life expectancy is assessed by means of PGLE due to stomach cancer. We calculated the gain in life expectancy due to the elimination of stomach cancer in the years 2005 and 2030. For each year, we prepared cause-elimination life tables using all-cause mortality rates for 2005 and using stomach cancer mortality rates for each respective projection year (2005 to 2030). The all-cause mortality rates were obtained from Eurostat. For Denmark, all-cause mortality rates were used from the Human Mortality Database (www.mortality.org). For each country, the same set of all-cause mortality rates was used over the years in order to maintain comparability between these years.

6.3. Results

Figure 6.1 shows trends in age-standardized mortality rates between 1980 and 2005. In all countries, stomach cancer mortality rates declined steadily. The average rate of decline is within a narrow range, from 3.61 percent per year for Norwegian men to 4.90 percent for Danish and Finnish women. The overall average rate of decline was 4.2 percent per year. The rate of decline remained similar over time for both sexes in most of these countries. There was no indication that the rate of decline (expressed in percent decline per year) had been levelling off in recent years. A main exception is the strong decline in mortality among Finnish women in the 1980's, when Finnish women were catching up with other countries.

In Figure 6.2, the rate of declines in stomach cancer mortality over the period 1980 to 2005 is plotted against the age-standardized mortality rates in 1980. The aim of this scatter plot is to assess whether the decline in stomach cancer mortality was higher in populations with higher initial mortality rates. However, both among men and women, no such positive association was found.

Table 6.1 presents projections for 2030 of stomach cancer mortality rates, absolute number of deaths, and potential gained in life expectancy (PGLE). Values projected for 2030 are compared to values observed for 2005 by means of ratios with 2005 as reference. In all seven European countries, age-standardized mortality rates would have declined in 2030 compared to 2005 if past trends were to continue. This decline would be substantial in all populations. Rate ratios are between 0.28 for Finnish women and 0.41 for Norwegian men, with an average

of 0.34. The latter value represents a 66 percent decline in age-standardized mortality rates between 2005 and 2030.

Similar declines were observed in terms of PGLE. This implies that, in terms of its effect on life expectancy, the importance of stomach cancer would decrease by about two thirds between 2005 and 2030.

The decline in the absolute number of deaths would be substantial as well, although with more variability between countries. Rate ratios would be between 0.38 for Danish women and 0.73 for Norwegian men, with an average of 0.48. The latter value implies that the absolute number of stomach cancer deaths would decline by 48 percent despite the ageing of the national populations.

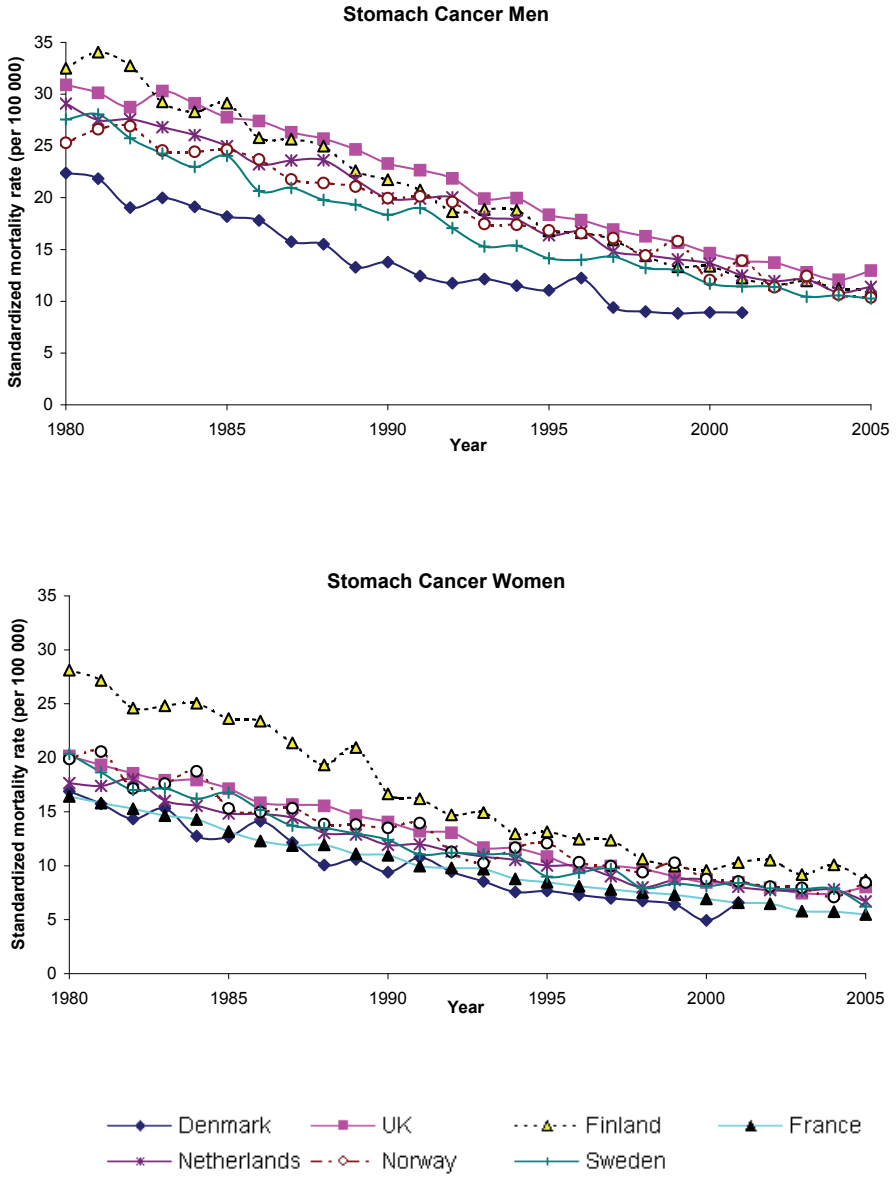

Figure 6.1- Age-standardized stomach cancer mortality rates (per 100,000) in seven European countries by sex: 1980-2005 *

* Corresponding estimates of annual declines (%) for men (women) are for Denmark 4.60 (4.90), United Kingdom 3.96 (4.16), Finland 4.68 (4.90), France Metropolitan 3.67 (4.32), Netherlands 3.92 (3.81), Norway 3.61 (3.90), and Sweden 4.06 (4.11).

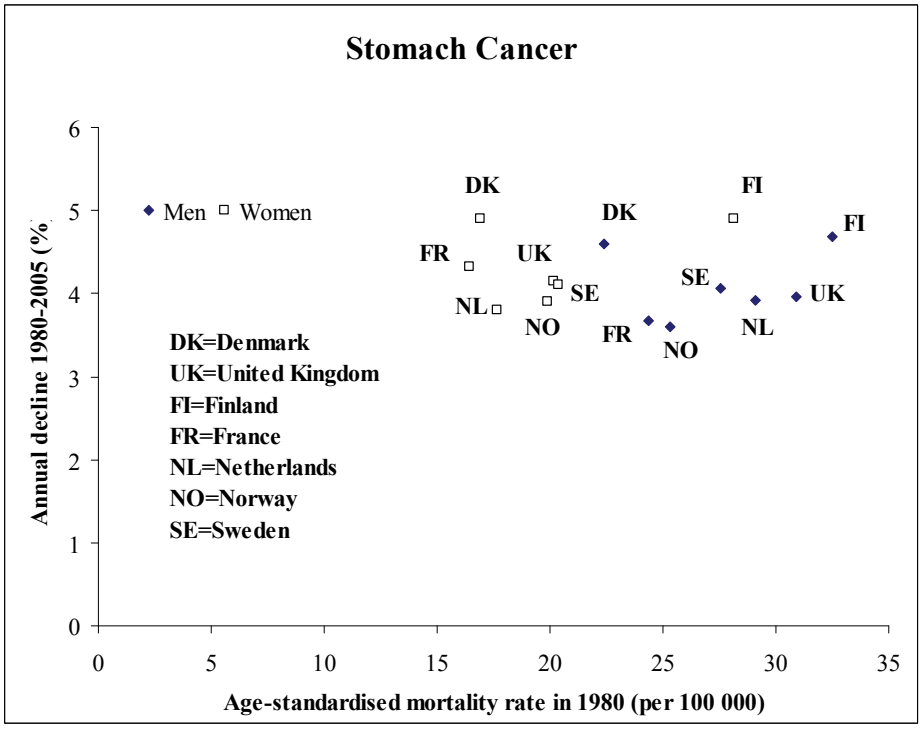

Figure 6.2- Annual declines (%) in stomach cancer mortality 1980-2005 against age-standardized mortality rates in 1980, by sex and country

Table 6.1– Stomach cancer mortality rates (age standardized, per 100,000), absolute number of deaths, and potential gained in life expectancy (PGLE), by country and sex, for 2005 (observed) and 2030 (projected)

	Year	Country						
		Denmark	United Kingdom	Finland	France	Netherlands	Norway	Sweden
Men								
Mortality rates	2005	7.22	12.95	11.09	9.87	11.40	10.37	10.27
	2030	2.23	4.36	3.20	3.80	4.00	4.28	3.50
	2030/2005 *	0.31	0.34	0.29	0.39	0.35	0.41	0.34
Number of deaths	2005	204	3914	301	3045	963	242	470
	2030	95	2117	156	1880	580	177	241
	2030/2005	0.47	0.54	0.52	0.62	0.60	0.73	0.51
PGLE	2005	33.45	60.99	58.47	54.43	60.13	52.36	46.36
	2030	10.36	20.54	16.67	21.01	21.10	21.61	15.76
	2030/2005	0.31	0.34	0.29	0.39	0.35	0.41	0.34
Women								
Mortality rates	2005	4.59	8.02	8.69	5.49	6.70	8.44	6.22
	2030	1.32	2.44	2.46	1.80	2.67	2.69	2.42
	2030/2005	0.29	0.30	0.28	0.33	0.40	0.32	0.39
Number of deaths	2005	127	2475	240	1789	566	196	284
	2030	48	1066	100	872	335	91	146
	2030/2005	0.38	0.43	0.42	0.49	0.59	0.47	0.51
PGLE	2005	22.84	37.85	52.78	36.95	39.24	48.92	31.35
	2030	6.76	11.74	14.53	12.10	15.92	15.64	12.58
	2030/2005	0.30	0.31	0.28	0.33	0.41	0.32	0.40

* The figure for 2030 divided by the related figure for 2005.
For Denmark, the values for 2005 are not observed but projected.

6.4. Discussion

The strong decline in stomach cancer mortality was found to continue at an undiminished rate until 2005 in each of the seven European countries. If this decline were to continue into the future, stomach cancer mortality rates would decline with about 66 percent between 2005 and 2030. A two-thirds decline would also be observed in terms of the effect of stomach cancer on people's life expectancy at birth. The absolute number of stomach cancer deaths would diminish by about 50 percent despite the ageing of national populations. Thus, by extrapolating the strong, stable and consistent mortality declines in recent decades, stomach cancer was projected to become increasingly less important as a cause of death in Europe in the next decades.

A key factor for the past declines in stomach cancer mortality is a decrease in the exposure to *Helicobacter pylori* infection [23]. *H. pylori* prevalence had been found to decline in parallel with the decrease of incidence of stomach cancer [24]. However, *H. Pylori* infection may not be the only factor. It has been estimated to account for only half of the global total burden of stomach cancer because of synergistic or antagonistic roles of dietary and other exogenous factors [25]. Complementary explanations for the observed declines in stomach cancer mortality may include better food preservation and refrigeration, improvement in environmental conditions and lifestyle changes [27,26].

Improved medical treatment may also have contributed to the decline in mortality from stomach cancer [26, 27] like it contributed to the observed differences in stomach cancer mortality between European countries [27]. This role is supported by the observation that, while the incidence of stomach cancer had declined as well, mortality rates seemed to have declined at faster rates, indicating a decline in case fatality rates [14]. Therefore, further advances in the treatment for stomach cancer and *H. pylori* infections may be important to maintain a strong decline in stomach cancer mortality rates in the future. However, declines in the near future may still be largely driven by recent improvements in the living conditions that current generations had experienced during their childhood and adulthood.

Empirical support for the expectation that the decline in mortality from stomach cancer will continue in the future comes from the trends that were observed for the past 25 years. Firstly, there is a strong consistency in the recent trends in stomach cancer mortality among both sexes and among each of the seven European countries. Second, these declines had persisted up to recent years in each of these populations, including those with the lowest initial mortality rates. Furthermore, steady declines in stomach cancer mortality were observed in the middle-aged and the young population as well, suggesting that they are likely to continue in the near future [4, 5, 16]. The latter observation is consistent with observations of cohort-wise patterns of decline in stomach cancer mortality in

European countries [28] [14, 29], which may reflect the effects of improvement in living conditions in childhood [28].
It should be emphasized that, even though future declines may seem likely, our study was primarily aimed at exploring possible future trends by extrapolating past trends. This extrapolation provides a baseline scenario against which new studies may formulate more specific scenarios of future trends. For example, policy-based scenarios may focus on the potential effects of specific preventive policies or advancement in the treatment of stomach cancer. As the stomach cancer may become ever less important in terms of mortality, scenario studies will need to also include measures of incidence, prognosis and prevalence of stomach cancer.

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7

General discussion

General Discussion

This final chapter first briefly addresses the research questions of this thesis, and evaluates the methodological approach in obtaining these results. Subsequently, it elaborates on the general background of observed trends, the role of IMR and GDP as explainers for cohort mortality, and the potential of eternal improvement of mortality risks. Next we discuss briefly the choice for IMR and GDP as proxy for living conditions relevant for health, and at some length the extrapolation methods. We end with, some recommendations for future care and research.

7.1. Main findings

7.1.1. Past trends

The first research question addressed the past trends in mortality of IHD, stroke and stomach cancer in seven European countries. In general, we observed an overall decline in mortality from these three diseases from 1950 to 2005 in all countries, for all ages and both men and women, with the important exception of a period epidemic of IHD in 1950 to 1970. From a cohort perspective, we observed steady declines for cohorts born between 1860 and 1939 in most causes, again with the exception of IHD.

Ischemic Heart Disease (IHD) mortality increased between the 1950s and 1970s in all countries for both men and women, except for younger women in France and Finland. This increase was generally followed by a decline between the 1970s and 1990s, in particular among younger people. In most countries, the decline started earlier among women than among men. However, in all countries, the decline was slightly larger for men, in particular in the Netherlands, Sweden and Denmark. The overall decline persisted until 2005, with no consistent evidence for a deceleration.

Mortality from stroke declined from the 1950s to the 1990s in all age groups, and both sexes, in most countries, often with larger declines in more recent decades. The rate of these declines greatly differed according to birth cohort, country and sex, with mostly higher declines for the youngest birth cohorts, suggesting cohort effects related to possibly the smoking epidemic. Relatively strong declines were observed in France, compared to smaller declines in Sweden. The observed declines persisted until 2005.

In all countries, stomach cancer mortality rates declined steadily for all birth cohorts, all ages, and both sexes. The smallest decline was observed in Norwegian men and the largest decline in Danish and Finnish women. In particular in the 1980s, the Finnish mortality declined to attain levels as in other countries. The rate of decline remained similar over time in most of other countries. The decline in stomach cancer over successive cohorts was generally

stronger among women than among men. For both sexes, the observed declines persisted until 2005.

7.1.2. The impact of IMR/GDP

The second research question was on the role of living conditions in early childhood. We often observed strong relationships with measures of living conditions (IMR and GDP) with cohort-specific trends in mortality from stroke or stomach cancer. However, past changes in living conditions in childhood were not always consistently related to cohort-wise trends in either stroke or stomach cancer mortality.

Before discussing these results in more detail, we first summarise the time tends of the two determinants between 1860 and 1940. Infant mortality rate (IMR) showed a general tendency to decline, especially after 1900, a tendency that started much later in some countries (e.g. Denmark and England & Wales) than in others (e.g. The Netherlands). Regarding Gross Domestic Product (GDP), a general increase can be observed for all countries.

For stroke, when data for all countries are pooled, and associations across countries are also taken into account, the overall correlation between IMR and mortality is strong. This strong association with stroke mortality may reflect the relation between early life factors and adult hypertension, which is rather strong [1] and which in turn may contribute to associations with stroke mortality. In separate analyses in which we made comparisons across countries, instead of across birth cohorts, the relationship was slightly positive when comparing countries for birth cohorts born before 1900. However, for birth cohorts born after 1900 this association was slightly negative. This inconsistency in patterns will be discussed below.

The relationship of IMR to IHD mortality is more complex. A variable and sometimes inverse relationship was observed in different countries. After pooling all countries, and also taking into account the associations across countries, the overall correlation with IMR was not significant for IHD mortality. Clearly the 'epidemics' of IHD - of which the rise and fall still are ill-understood [2, 3] - do not parallel the ending of the 'epidemics' of IMR.

A strong association was found between stomach cancer and IMR across different cohorts in all countries. We also studied GDP in relationship to stomach cancer. For GDP and stomach cancer, a strongly negative association existed at all ages. The association between stomach cancer mortality and GDP at birth was stronger for older ages. When the different countries are pooled, the overall correlation with stomach cancer mortality was positive for IMR and negative for GDP at the time of birth. However, irregularities in time trends for GDP did not neatly parallel the irregularities in the decline in mortality for stomach cancer. The lack of an entirely consistent relationship is discussed below.

7.1.3. Future trends if past trends were to continue

The third research question was on future trends in the burden of mortality of the three diseases. Scenarios were formulated based on extrapolation of recent trends in mortality. According to the extrapolation-based scenarios, both IHD and stroke will lose much of their importance as causes of premature death in the near future. And this applied even more so for stomach cancer, which was projected to become a minor cause of death in Europe by 2030. We also demonstrated that trends are similar in terms of Potential Gained in Life Expectancy (PGLE), but much less favourable in terms of absolute numbers of deaths.

In all seven European countries, age-adjusted IHD mortality rates would substantially decline until 2030 if past trends were to continue. In general, trends between 1980 and 2005 showed annual mortality declines of about 3.5% in men and 2.5% in women for IHD; while stroke and stomach cancer declines continued at annual rates of about 3% and 4%, respectively (with small differences for gender). Projected on the relevant populations, during 2005-2030 an overall decline would be observed in IHD mortality of 40-60 % in men and 30-55% in women, in stroke mortality of 25-70% in men and 20-60% in women, and of 60-75% for stomach cancer mortality. As projected trends slightly differed among the seven European countries, with generally large decline in countries with higher mortality levels at onset, these projected changes would generally result in cross-national convergence of mortality rates in 2030.

The projected trends in mortality rates are, given the ageing populations, different when evaluated in terms of absolute deaths. The absolute number of deaths for IHD and stroke will decline slowly or even increase at the longer run. This warns that declining age-specific mortality rates do not imply that the future number of deaths from the three important diseases must decline. Rather, future deaths will occur later in life.

Meanwhile, the declines in PGLE are only slightly different from the age-adjusted mortality rates. The projected declines are up to 5% stronger compared to the mortality rates. This slightly larger increase reflects relatively large decline in mortality at younger ages, and expected rises in the life expectancies of the European populations.

7.2. Discussion of principal findings

Here we provide some comments on three issues: explanation of past trends, the tenability of the general relation of IMR/GDP with mortality trends, and the issue of the 'eternal improvement' in mortality.

7.2.1. Explanation of past trends

A key issue is whether the observed declines in mortality are due to declines in the incidence of diseases and/or in their case-fatality. In developed countries, both the incidence and mortality of IHD and stroke continued to decline in both sexes in recent decades [4-6]. However, for IHD and stroke, there is evidence for declines in case-fatality as well. Incidence decline may be determined by changes in the cardiovascular risk factor profile in the community, while variations in case fatality rate can be explained directly by changes in medical care and indirectly by changes in the severity of the disease [7]. The declining case fatality may be due in particular to advances in diagnosis and treatment [8, 9] including rapid dissemination of CT and MRI technology since 1970s [10].

The classic risk factors might not be the largest contributors to the observed trends in mortality and incidence, as societal factors [11] and environmental changes [12] do matter too. In addition, attributing the falls in mortality to risk factor changes or effective medical interventions separately is difficult because favourable trends in both have occurred simultaneously. In a computer-simulation model, Hunink found that primary and secondary risk factor reductions of IHD mortality explain about 50% of the decline in USA but that more than 70% of the overall decline in mortality has occurred among IHD patients [13]. On the other hand, Unal concluded that compared with secondary prevention, primary prevention (especially tobacco control and healthier diets) achieved a fourfold larger reduction in deaths in England and Wales [14]. In a study in Finland, the contribution of different factors in mortality decline for both genders were estimated to be about 8.8% (smoking), 37% (high cholesterol), 7.5% (high blood pressure), 53.3% (three risk factors combined), and 23.1% (treatment) for stroke mortality decline [15].

In spite of declining incidence rates, stomach cancer is still the *second* most important cause of death from cancer worldwide [16], with an overall rate close to lung cancer. Improvements during the 20th century in environment and nutrition may have resulted in a gradually lower incidence of stomach cancer, while more accessible and effective facilities for cancer therapy may have helped to reduce its case fatality [17]. Changes in diagnosis and treatment may have made a contribution to the declining incidence and mortality rates of stomach cancer [18, 19]. Factors related to treatment and general management of cancer patients are also expected to be important, as they for example explain part of variability in survival between European countries [20, 21].

7.2.2. IMR/GDP and mortality

Despite the fact that many of the relations between the three diseases and IMR/GDP were as expected, some irregularities were observed (see also above), in particular for IHD and stomach cancer.

The cohort-wise decline in IHD mortality shows a hill-like shape, which disturbs the relation with the universally declining IMR. After an initial decline, there is for decades a temporary increase which, together with the subsequent decline, can be described as the rise and fall of the IHD epidemic in general. The causes of this epidemic are not entirely understood. The smoking epidemic is an insufficient explanation, if only because the smoking epidemic affected men and women in very different ways, whereas the timing of the IHD epidemic was similar for both sexes. Some have pointed to the potential role of adaptation to an entire different life and food pattern during the first half of the 20th century [22, 23].

In addition, period-wise changes in medical care may have confounded the study of the associations between IHD mortality trends and early life factors. These associations may have been obscured amongst others by large changes in effective medical care during the second half of the 20th century [22, 23]. In stroke and stomach cancer, change in care may have been more gradual, although the invention and introduction of life saving therapies (ambulance transport, CCU, thrombolytics, etc) may also have introduced large period-wise changes in some of the countries studied.

Even though IMR and stroke were strongly related, the irregularities in the decline in IMR did not clearly correspond to similar irregularities in the decline in stroke. Stroke mortality levels were relatively stable in birth cohorts from 1860 to 1880, but declined in subsequent cohorts, but not as rapidly as IMR. We can only speculate about why the general IMR improvement did not translate as quickly into a cohort-wise decline in stroke mortality. It could be the case that late IMR improvement is based on factors with broader health effects (with lasting effects also on stroke incidence and mortality) compared to the factors most important earlier in IMR improvement (e.g. reduction of exposure through new sewerage systems). Or, the elderly population in general changes over time, with a more heterogeneous group entering old age in later cohorts, which in turn may change the time relation between initial IMR and stroke mortality in later birth cohorts.

For stroke mortality, another confounding factor may have been introduced by the rapid decline in IHD mortality. It was hypothesized that the course of the IHD epidemic has influenced trends in stroke mortality. If less people die from IHD, and if survivors have generally a higher exposure to risk factors for stroke, this would act to increase incidence from stroke. However, this hypothesis was not supported by a study of Peeters et al [24].

Several studies have shown the association between IHD and adverse living conditions in early life [25-29], but not always [2, 3]. For stroke, some studies

have observed this relationship [28, 30], whereas others have not [26, 29]. We believe that our own findings, which are not fully consistent either, deserve further study with systematic data on IHD and stroke treatment added to data on trends in incidence and mortality. For the moment, the discrepancies that we observed between IMR trends and trends for IHD and stroke mortality warns against too strong statements regarding an overriding effect of early life conditions on population-wide trends in these diseases.

Our study suggested the importance of "environment" in early life in determining the risk for stomach cancer [16, 31], in particular childhood social circumstances [32-34]; which is consistent with the strong geographical correlation between mortality from stomach cancer in adulthood and infant mortality around the time of birth [3, 35]. However, some of our results indicate that the secular trends in stomach cancer are not neatly related to trends in IMR, suggesting that mortality trends were partly determined by changes in adult socioeconomic circumstances and lifestyles, rather than childhood [17].

7.2.3. Future trends: eternal improvement?

Our predictions are based on the assumption of a continued reduction of age-specific mortality rates with the same tempo as observed in recent decades. Such an assumption in our view is plausible given fact that recent changes are linked, not just to advances towards more efficacious medical treatment, but also to a growing awareness on the part of the general public regarding of the crucial role played by life style (including dietary habits and smoking). This awareness, which prevails among more recent, well-informed and better educated cohorts, essentially represents an investment in the future, by decreasing the accumulation of risks known from the older cohorts. The evidence supporting this hypothesis is suggestive: decreasing prevalence of cigarette smoking [36], decreasing use of butter on bread and increasing use of vegetable oil in cooking [36], and decreasing cholesterol levels and hypertension [36], which in turn could be related to better medical control of biological risk factors [37]. We also expect a contribution from the introduction of new treatments and the increased uptake of and compliance to existing treatments, and better access with fewer persons untreated [38].

Is this continued improvement yielding eternal life? While the increase in life expectancy was largely propelled by the decline in infant and child mortality up until the middle of twentieth century, it has since then been sustained by the decline in mortality among elderly people, in particular through better survival from cardiovascular diseases and some cancers, thanks to progress in medical care [39].

Therefore, at one hand, further improvement may here be expected through the further improvement of medical care which - as we believe - is far from exhausted; to this we add the permanent improvement of the living environment: the impressive change in work and working conditions, and the better conditions

at life's start. Part of this improvement will rest on the ability to attain better outcomes among socioeconomic groups who are worse off.

On the other hand, levelling off of this improvement may perhaps be expected from the inevitable greater role of comorbidity at higher age. In elderly patients with heart diseases, the high prevalence of non-cardiovascular comorbidity may affect prospects for substantial improvements of the survival of patients. Obesity (overweight) might also be so important to take into account, because of direct or indirect effects [40, 41]. It should be noted that secular trends toward increasing prevalence of obesity have been occurring also in childhood [42]; thus, the evidence of increasing mean values of BMI in the adult population suggests the importance of preventive measures at earlier ages [43]; which in turn suggests necessity of further improvement of dietary patterns and reduction of physical inactivity for prevention of obesity at the population level. To the extent that we succeed in reducing comorbidity through lifestyle related diseases, we may hope to prevent a leveling off of the mortality decline in the near future. For stomach cancer, future speculation should most likely differentiate between adenocarcinoma of the cardia, and subcardia cancers, where adenocarcinoma of the cardia might follow a similar trend as oesophageal adenocarcinoma. The different relation to comorbidity (e.g. adenocarcinoma of the cardia is related to hypertension, subcardia cancer to other comorbid diseases) suggests at least some etiological heterogeneity, which easily translates in different future development [44].

The trend towards improvement does not represent a physical law but is the result of human endeavours. A sustained positive direction of future trends will therefore require support from public health policies directed towards maximal use of the available preventive options, but also towards the full use of clinical care options for those with a chronic disease.

7.3. Methodological issues

Here we take opportunity to discuss two issues for which are not addressed to a full extent in the separate papers: the measurement of early life conditions, and the choice of a forecasting method**.**

7.3.1. The measurement of early life conditions

In our analysis, the IMR and GDP were used as indicators of general conditions of living in different periods, and indeed provided a partial explanation of long-term changes in mortality at adult ages.

The choice for these indicators was based on expected relevance and on the availability and comparability of data for seven European countries over a long period of time. For a possible alternative indicator, body length, continuous historical time series were only available for four countries [45]. It should be

acknowledged that both IMR and GDP are only approximate indicators of the concept of "general living conditions"[46]. Nonetheless, the IMR is one of the most important indicators of social development and health [47, 48].

The correspondence between the findings for IMR and those for GDP suggest that improvement in general living conditions in childhood are modestly related to the secular decline in stomach cancer mortality in western European countries. However, it is important to recognize that both our measures of general living conditions in childhood cannot measure in detail all specific elements that may be relevant for stomach cancer. For stomach cancer, which is strongly related to *H. pylori* infection in early life, we would need to acquire data on the prevalence of *H. pylori* infection in childhood in the different birth cohorts. These data were not available for any of the countries considered.

7.3.2. The choice of a forecasting method

In this section, we first discuss the classification of forecasting methods and then continue with an inventory of the methods used in different projection studies. We end this section by a summary of the main results obtained with some of the projections studies.

7.3.2.1. Classification of forecasting methods

To make future projections, besides the extrapolation of the past trends, a variety of models have been applied [49-53]. For example, APC models have been applied to stroke mortality in Sweden [7], disease-state simulation models to IHD incidence, mortality and cost in USA [54] and to heart disease in the Netherlands [55], whereas risk-factor based model was applied to the projection of incidence of myocardial infarction (MI) in Australia [56]and in Sweden [39].

Several authors discussed the classification and naming of predictive mortality models. Olshansky divided forecasting methods into two categories, namely methods based on extrapolation and procedures based on mortality in a more 'advanced' populations [57]. Manton suggests a classification into empirical or extrapolation procedures and explicit procedures based on theories of human mortality and ageing [58, 59]. Willekens distinguishes extrapolation methods and methods based on epidemiological and biomedical research, and suggests that forecasting should go from pattern-oriented to process-oriented forecasts [60]. This suggestion has also been discussed by European Association for Population Studies which concluded that it seems inevitable to continue forecasting using extrapolation [61]. Wilmoth concluded that the most reliable method for predicting the future mortality remains to extrapolate past trends [62].

7.3.2.2. Previous forecasting studies

Here we present the most important projection studies using a variety of forecasting/projection methods. We distinguish four basic models including incidence-alone models, mortality-alone models, incidence-mortality models, and incidence-prevalence-mortality models. Depending on the data analysis underlying the study, we can further divide these models into age-period (AP), age-cohort (AC), or age-period-cohort (APC). Models may use regression approaches or simulation models. Gender is always added as an explanatory or stratifying variable. Table 7.1 summarizes the methods and results of these projection studies.

Table 7.1- Summary of projection studies

Type of projection	Model	Author (year)	Purpose of projection (disease)	Place, Time and Data	Key results
Incidence- alone	AP using regression	Malmgren [63] (1989)	Future burden of long-term care of patients (stroke)	England and Wales, Up to 2023, Population-based study in 1983 using incidence and disability data	Increased burden of health care of patients with first ever strokes in 2023
Mortality- alone	AP and APC using regression and (cause-elimination) life table	Amiri (2010)	Future death and PGLE (IHD, stroke, stomach cancer)	Seven European countries, 1950-2000, 1980-2005, up to 2030, Mortality data (historical and Eurostat data)	IHD, stroke and stomach cancer will lose much of their importance as causes of premature death in the near future
	AP using regression	Gondos [64] (2009)	Survival trends (15 common cancers)	11 European populations, 2005-2009, Based on data of 1990-1994 and 2000-2004	The importance of care in future
	APC using regression	Quinn [65] (2003)	Examine mortality trends (cancers)	20 EU countries, Up to 2015, WHO Cancer mortality data 1950s-2000	Survival estimates for 2005-2009
	APC using regression	Huovinen [66] (2006)	Predict future mortality (IHD)	Finland, Up to 2030, data from Finnish official statistics	Future importance of people 80 and more
	AP and APC using regression	Caselli [67] (2006)	Comparison of extrapolation methods; i.e. AP, APC and regression (cardiovascular and cancers)	England and Wales, Up to 2050, data on population 60 to 85 years 1950 to 2000	APC reproduces reality (highest quality).AP for changing trends (less validity)
	AP using regression	Sonnenschein and Brody [68] (2005)	Project the effect of ageing on future mortality (heart diseases and cancers)	USA, Up to 2050, Data of 1999 US census	Ageing will increase heart diseases and will decline cancers
Incidence-Mortality	AP using (multi)state-event transition	Niessen [69] (1993)	Determine the range of incidence and fatality decline (stroke)	The Netherlands, 1985-2005, Data of 1979 to1989 on national hospital admissions and mortality rates	Survival increase and population ageing could partly explain the declines

	AC using regression	Bonneux and Looman [70] (2003)	Predict future health care needs (IHD)	The Netherlands, Up to 2015, Dutch data on number of deaths and hospital admissions 1970 to 1999	Heart health care needs will increase among middle-aged women
	APC using regression	Murray and Lopez [71] (1997)	Projection of future health status (IHD, stroke, cancers and …)	47 countries, Up to 2020, Data of 1950 to 1990 in nine cause-of-death clusters	Future importance of ageing
Incidence-Prevalence-Mortality	AP using simulation	Dunning [72] (1987)	Examination of about 19 alternative scenarios including 3 scenarios for general lifestyle, 6 for acute care, 6 for chronic care, and 4 scenarios for patients' lifestyles (IHD)	The Netherlands, Up to 2010, Data on incidence, prevalence, and mortality of Dutch population in 1980	Future importance of life style changes
	AP using simulation	Bonneux [55] (1994)	To make a quantitative analysis of the heart disease epidemic by combining morbidity and mortality data of Framingham and project to Dutch population (IHD)	USA, Up to 2020, Framingham data	Increasing future morbidity and health care needs
	AP using a multistate life table	Struijs [73] (2005)	Determine future number of patients (stroke)	The Netherlands, Up to 2020, Dutch data	Increasing future number of stroke patients
IHD Projections	Dunning [72], Bonneux and Looman [70], Huovinen [66], and Sonnenschein and Brody [68]		General projection of an overall decline in IHD mortality in the future, due to medical improvements, with fewer declines (and even slightly increase) in older persons than middle-age people, as a result of ageing of population		
Stroke projections	Niessen [69], Struijs [73], and Malmgren [63]		An overall decline in stroke incidence and mortality in the future, but increase in the number of patients, due to the factors such as ageing of the population and an increase in cardiovascular survival leading to a further increase in major stroke prevalence among the oldest age groups,		
(Stomach) cancer projections	Quinn [65], Gondos [64], and Sonnenschein and Brody [68]		Fewer mortality from cancers in the future, due to decreasing age-specific mortality trends, more effective screening programs (on breast, cervical and colorectal cancers), on smoking prevention, and better treatments		

7.3.2.3. Evaluation of our own projection method

We would like to distinguish between 'static' regression-based methods like employed in our thesis, and more detailed 'dynamic' models. Dynamic models might result in more accurate results in the long run due to taking into account survival of patient's changes over time, the occurrence of events over time, and the health state transitions. To the extent that a disease model is used and the determinants and relations are included, including their time trends, such models allow for non-linear changes. However, for the same reason they have an intrinsically higher risk for misprojection as their need for specification of the causal pathways always requires several assumptions regarding mortality and morbidity, separating the modeled dynamics from the unspecified changes, and requiring detailed information about conditional probabilities on mortality and morbidity. The more a disease as a process is understood, and its determinants and changes thereof, and the more a disease safely can be regarded as 'isolated' from other diseases, the better the dynamic models may perform. However, the diseases of this thesis do not easily qualify for dynamic modeling: despite many papers with dynamic models, one might argue that without an adequate explanation of the cardiovascular epidemic at large, it is hazardous to rely on dynamic modeling. In view of this arguments, in this thesis, regression models have been used. We thereby followed Wilmoth's recommendation [62] and European Association for Population Studies [61] and our preference to using observed trends (not synthetic trends). Besides long-term morbidity data are unavailable, and the epidemiological knowledge on stomach cancer provides little opportunities for explicit modeling. We should also note that the projections used in this thesis are not *forecasts* in the literal sense, but *projections* that explore possible future trends on the basis of specific assumptions [74].

7.4. Recommendations

Our recommendations fall into two parts: policy implications and future research:

Policy implications

In view of future increase in future hospitalization numbers (not: age-specific rates) and the related demand for health care, we recommend that:

- The health care providers and insurance companies should be informed that they are facing increases in the future demand; as most likely the proportion of comorbidity of those contracting diseases will increase (in absolute terms due to the age shift), medical costs will rise even in excess of the mere increase of numbers.

- To achieve ongoing improvement especially in IHD and stroke, investments are required in prevention (primary, secondary) with special emphasis on decreasing treatments' gaps, as inequalities might set a limit to improvement in general.
- Further attention should be given to verification of stroke subtypes, because management and prevention strategies for different stroke types vary. Improvement in the quality of routinely available stroke mortality data is also important.
- Given the ageing population, particular attention should be given to covering all age groups but especially the oldest old. The priority of care for the studied diseases should be shifted from prevention of death to prevention of disability.

Future research

For future studies, we recommend the following research topics to pay attention to:

- The role of early life circumstances in mortality from IHD, stroke or stomach cancer; including the specific measurement of early life conditions including prenatal data; the explanation of the observed differences between populations in cohort-wise trends; and the study of migrants (first and second generations).
- In addition to the individual-based simulation forecasting models, the development of more robust population health projection models aiming to incorporate exogenous influences on the occurrence of disease and the effect of population-wide preventive measures.
- The pursuit of more cohort studies - like ERGO and LASA- including the oldest old with information to elucidate in more detail disease dynamics; and information about distribution of blood glucose concentrations, diabetes, hypertension and other risk factors, including genetic predispositions.
- For stomach cancer, future studies should determine the contribution of more specific factors, such as *H. pylori* infection, on top of (or instead of) general living conditions in early life.

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8

Summary

Summary

The aim of this PhD thesis was to describe long term trends in mortality from three diseases (Ischemic Heart Disease (IHD), stroke, and stomach cancer) in developed countries, to assess the relationship among these trends and early life conditions (measured by infant mortality rate (IMR) and gross domestic product (GDP) around the birth year), and to extrapolate the mortality from these three diseases until 2030, based on the observed mortality trends from 1980 to 2005.

We selected these three diseases because of the role of IHD and stroke as first and second leading causes of deaths, in spite of their declining trends in mortality in recent years; and the possible relation of stomach cancer with early life conditions and therefore potential cohort effects. In addition, as stomach cancer had only few adult risk factors in common with the other selected diseases, its study promised further insights into the effects of early life conditions.

We studied mortality from IHD, stroke, and stomach cancer with data from 1950 to 1999 (historical analysis) and from 1980 to 2005 (extrapolation base). We applied a life-course analytical perspective (focusing on both period and cohort effects), and we performed comparative studies among seven European countries, i.e., Denmark, England and Wales, Finland, France, the Netherlands, Norway, and Sweden.

Five datasets were used. For Chapters 2 and 3 we used three datasets, i.e. dataset A, B, and C respectively. Data of ***dataset A***, on IHD, stroke, and stomach cancer mortality and the population at risk, were obtained by year of death (1950-1999), sex, and five-year age group for Denmark, England & Wales, Finland, France, the Netherlands, Norway, and Sweden. For Denmark, Finland and Norway data were available only from 1951, and for Sweden, from 1952. For France, data were only available until the year 1997 and for Denmark, until 1998. These data were obtained from national statistical offices and related institutes. Data of ***dataset B***, on IMR, defined as the number of deaths during the first year of life per 1000 live-born babies, for the period 1860-1969. ***Dataset C*** consists of the data for GDP. To reconstruct trends in real national GDP, i.e. GDP expressed at constant 1995 prices in millions of national currency units, between 1865 and 1939, the historical national accounts data were used. For the Netherlands, these historical data were available only from 1900 onwards, and for the earlier years data on national accounts from Statistics Netherlands were obtained. For Chapters 4 to 6, we used ***dataset D***. Data on IHD, stroke, and stomach cancer mortality for Denmark (not for stroke in Chapter 5), Finland, France metropolitan, the Netherlands, Norway, Sweden and the United Kingdom on the number of deaths and corresponding numbers of population at risk, by sex and five-year age groups for the years 1980 to 2005 have been obtained from Eurostat

(Denmark from 1999-2001, France from 1998-2005). And finally, ***dataset E***, containing future population numbers, were used for projection, was obtained from Eurostat (baseline variant), except for Norway for which the data have been obtained from Statistics Norway (medium national growth variant).

The **first part** of this thesis, i.e., **Chapters 2** and **3**, describes the past mortality trends in IHD, stroke, and stomach cancer in seven European countries. In these chapters, the role of period and cohort effects in the observed trends in mortality between 1950 and 1999 was identified. Furthermore, we estimate the role of early life conditions and environmental factors (measuring with IMR and GDP at birth) to cohort-specific trends in mortality from IHD, stroke and stomach cancer.

Chapter 2 describes the trends of mortality from IHD and stroke in relation to infant mortality rate (IMR). We found that IHD mortality increased for successive cohorts up to 1900, and then started to decline. Stroke mortality levels were virtually stable among birth cohorts up to 1880, but declined rapidly among later cohorts. A strong positive association was found between cohort-specific IMR levels and stroke mortality rates. There were no strong cohort-wise associations between IMR and IHD mortality. These results support other studies in suggesting that living conditions in early childhood influence stroke mortality rates, also at the level of national populations, with potential differences among countries. Future studies should determine the contribution of specific early life factors to the recent declines in mortality from IHD and stroke.

In **Chapter 3**, we relate the secular trends in mortality from stomach cancer to trends in IMR and GDP. Our results showed large differences between successive birth cohorts in mortality from stomach cancer. In each country, these cohort differences were closely related to IMR and GDP levels at the time of birth. However, stronger associations were observed with measures of living conditions during later life. In comparisons between countries, stomach cancer mortality rates were not consistently related to national levels of IMR and GDP. As a result, general living conditions in childhood did not seem to have had a predominant effect on secular trends in stomach cancer mortality. The mortality decline is likely to be related to more specific factors, such as declining *H. pylori* prevalence.

In the **second part** of the thesis, **Chapters 4 to 6**, the future trends in mortality from the above mentioned disease are explored by projecting the mortality trends until 2030, based on the observed mortality trends between 1980 and 2005 in seven European countries. The projected mortality rates, the absolute numbers of deaths, and the potential years of life lost (PYLL) in 2030 are compared to the corresponding figures in 2005.

Chapter 4 illustrates the possible declines in IHD mortality in seven European countries until 2030. In all countries, IHD mortality rates among both

sexes declined incessantly from 1980 until 2005. Age-adjusted mortality rates would have declined by about 50 percent in 2030 as compared to 2005 if these past trends were to continue. The impact of IHD on life expectancy at birth would decline by about 25 to 50 percent in most populations. The absolute numbers of IHD deaths would decline slowly or even increase in some countries, because of population ageing. In conclusion, if current IHD mortality trends would continue, IHD would lose much of its importance as a cause of premature death in the near future.

In **Chapter 5**, we extrapolate the future trend of mortality from stroke. In all countries, stroke mortality rates declined incessantly until 2005 among both men and women. If these trends were to continue, age-adjusted mortality rates would decline by about one half between 2005 and 2030, with larger declines in France (about two thirds), and smaller declines in the Netherlands, Denmark and Sweden (about one quarter). Similar rates of decline would be observed in terms of PYLL. Because of population ageing, the absolute number of stroke deaths would decline slowly in United Kingdom and France, and stabilize or even increase in other countries.

In **Chapter 6**, we explore possible future trends in mortality from stomach cancer until 2030. Stomach cancer mortality rates declined between 1980 and 2005 at about the same rate (3.6-4.9 percent per year) for both men and women in all countries. The rate of decline did not level off in recent years, and it was not smaller in countries with lower overall mortality rates by 1980. If this decline were to continue into the future, stomach cancer mortality rates would decline with about 66 percent between 2005 and 2030 in most populations. A two-thirds decline would also be observed in terms of PYLL, while the absolute number of stomach cancer deaths would diminish by about 50 percent. Thus, in view of the strong, stable and consistent mortality declines in recent decades, stomach cancer is likely to become increasingly less important as a cause of death in Europe in the future.

Chapter 7, summarizes the main results, and elaborates on the determinants of the mortality decline in early life in the past and possible projections in the coming years. We concluded that cohort-wise patterns of decline in mortality were found, with some irregularities over the time, for each of the three diseases and in all countries. Our findings support the expectation of an association between changes in living conditions in early childhood and changes in population levels of stroke mortality. However, no strong evidence was observed for IHD or for stomach cancer mortality. If current IHD and stroke mortality trends would continue, they would lose much of their importance as the causes of premature death in the near future. The same applies, but to even a larger extent, to stomach cancer mortality. Especially for IHD and stroke, their incidence and disabling impact might decline to a much lesser extent. As a result, the prevention of IHD or stroke related disability instead of mortality may become increasingly important in the future.

Samenvatting

Het doel van dit proefschrift was om lange termijntrends in mortaliteit als gevolg van drie ziekten (Ischemic Hartziekte (IHD), cerebrovasculair accident en maagkanker) in ontwikkelde landen te beschrijven, om de relatie tussen deze trends en vroege levensomstandigheden te evalueren (door kindersterftecijfer (IMR) en bruto binnenlands product (GDP) rond het geboortejaar gemeten) en om de mortaliteit van deze drie ziekten te extrapoleren tot 2030, op basis van de geobserveerde mortaliteitstrends van 1980 tot 2005.

Wij selecteerden deze drie ziekten vanwege het belang van IHD en cerebrovasculair accident als eerste en tweede doodsoorzaken, ondanks hun afnemende trends in mortaliteit in recente jaren; en de mogelijke relatie tussen van deze ziekten en maagkanker met vroege levensomstandigheden. Bovendien, omdat maagkanker slechts weinig risicofactoren op volwassen leeftijd gemeenschappelijk heeft met de andere geselecteerde ziekten, kan bestudering ervan meer inzicht verschaffen in effecten van vroege levensomstandigheden.

Wij hebben de mortaliteit van IHD, cerebrovasculair accident en maagkanker bestudeert met behulp van gegevens van 1950 tot 1999 (historische analyse) en van 1980 tot 2005 (als basis voor extrapolatie). Wij pasten een levensloop perspectief toe die zich op zowel periode- als cohortresultaten concentreert. Bovendien maakten wij een vergelijkende studies tussen zeven Europese landen, d.w.z., Denemarken, Engeland en Wales, Finland, Frankrijk, Nederland, Noorwegen en Zweden.

Er werden vijf datasets gebruikt. Voor hoofdstuk 2 en 3 hebben wij drie datasets gebruikt, namelijk dataset A, B en C. Gegevens van ***dataset A***, met betrekking tot IHD, cerebrovasculair accident, maagkankermortaliteit en de risicopopulatie, werden verkregen naar jaar van overlijden (1950-1999), geslacht en 5-jaars leeftijdsgroepen voor Denemarken, Engeland & Wales, Finland, Frankrijk, Nederland, Noorwegen en Zweden. Voor Denemarken, Finland en Noorwegen waren de gegevens alleen vanaf 1951 beschikbaar en voor Zweden vanaf 1952. Voor Frankrijk waren de gegevens beschikbaar tot en met 1997 en voor Denemarken tot en met 1998. Deze gegevens werden van nationale statistische organisaties en gerelateerde instituten verkregen. Gegevens van ***dataset B***, met betrekking tot IMR, gedefinieerd als het aantal overlijdens gedurende het eerste levensjaar per 1000 levendgeboren baby's, werden voor de periode 1860-1969 verkregen. ***Dataset C*** bestaat uit de gegevens voor GDP. Om trends in reëel nationaal GDP te reconstrueren, d.w.z. GDP uitgedrukt in constante 1995 prijzen in miljoenen van nationale munteenheden tussen 1865 en 1939, werden de historische nationale rekeningsgegevens gebruikt. Voor de hoofdstukken 4 tot 6 hebben wij **dataset D** gebruikt. Gegevens over IHD, cerebrovasculair accident en maagkankermortaliteit voor Denemarken, Finland, continentaal Frankrijk, Nederland, Noorwegen, Zweden en het Verenigde

Koninkrijk over het aantal doden en overeenkomstig aantal personen dat risico loopt, per geslacht en 5-jaars leeftijdsgroepen voor de jaren 1980 tot 2005 zijn van Eurostat verkregen. En ten slotte ***dataset E***, die toekomstige bevolkingsaantallen bevat, werd van Eurostat (basis variant) verkregen, behalve voor Noorwegen, waarvoor de gegevens van Statistiek Noorwegen zijn verkregen.

Het **eerste deel** van dit proefschrift, d.w.z., **Hoofdstukken 2** en **3**, beschrijft de mortaliteitstrends uit het verleden voor IHD, cerebrovasculair accident en maagkanker van zeven Europese landen. In deze hoofdstukken is de rol geïdentificeerd van periode- en cohortpatronen in de geobserveerde trends in mortaliteit tussen 1950 en 1999. Verder schatten wij de rol van vroege levensomstandigheden (gemeten met IMR en GDP bij geboorte) bij cohort-specifiek trends in mortaliteit van IHD, cerebrovasculair accident en maagkanker.

Hoofdstuk 2 beschrijft de trends in mortaliteit van IHD en cerebrovasculair accident in relatie tot het kindersterftecijfer (IMR). Wij vonden dat IHD mortaliteit voor opeenvolgende cohorten tot 1900 toenam en daarna begon af te nemen. Sterfte aan cerebrovasculair accident was praktisch stabiel onder de geboortecohorten tot 1880, maar nam snel af onder latere cohorten. Een sterke positieve relatie werd gevonden tussen cohort-specifiek IMR niveaus en Cerebrovasculair accident sterftecijfers. Er waren geen sterke cohortwijze relaties tussen IMR en IHD mortaliteit. Deze resultaten steunen andere studies in de suggestie dat omstandigheden in de vroege kindertijd invloed hebben op sterfte aan cerebrovasculair accident, ook op het niveau van nationale populaties. Toekomstige studies zouden de bijdrage van specifieke vroege levensfactoren aan de daling van mortaliteit van IHD en cerebrovasculair accident moeten vaststellen.

In **Hoofdstuk 3** hebben wij de seculiere trends in mortaliteit van maagkanker aan trends in IMR en GDP gerelateerd. Onze resultaten toonden grote verschillen tussen opeenvolgende geboortecohorten in mortaliteit van maagkanker aan. In elk land waren deze cohortverschillen gerelateerd aan IMR en GDP niveaus ten tijde van de geboorte van opeenvolgende cohorten. Echter, sterkere associaties werden geobserveerd met indicatoren van levensomstandigheden gedurende latere leeftijd. In vergelijkingen tussen landen hingen maagkankersterftecijfers niet consistent samen met nationale niveaus van IMR en GDP. Dientengevolge lijkt het dat algemene levensomstandigheden geen overheersend effect hebben gehad op seculiere trends in maagkankermortaliteit. De mortaliteitsafname is waarschijnlijk gerelateerd aan meer specifieke factoren zoals het verminderen van het voorkomen van *H. pylori*.

In het **tweede deel** van het proefschrift, **Hoofdstukken 4 tot 6**, worden de toekomstige trends in mortaliteit van de bovenstaande ziekten geëxploreerd door de mortaliteitstrends tot 2030 te projecteren, gebaseerd op de geobserveerde mortaliteitstrends tussen 1980 en 2005 in zeven Europese landen. De geprojecteerde sterftecijfers, het absolute aantal overlijdensgevallen en de potentiëel winst in levensverwachting (PGLE) in 2030 zijn vergeleken met de overeenkomende cijfers voor 2005.

Hoofdstuk 4 beschrijft de mogelijke afname van IHD mortaliteit in zeven Europese landen tot 2030. In alle landen daalde de IHD mortaliteit onder beide geslachten onophoudelijk tussen 1980 en 2005. Voor leeftijd gecorrigeerde sterftecijfers zouden zijn afgenomen tot ongeveer 50 procent in 2030 in vergelijking met 2005 indien deze recente trends zich zouden voortzetten. De invloed van IHD op levensverwachting bij de geboorte zou met ongeveer 25 tot 50 procent afnemen in de meeste populaties. Het absolute aantal gevallen van sterfte aan IHD zou langzaam afnemen of zelfs toenemen in sommige landen door vergrijzing van de bevolking. Concluderend, als huidige IHD mortaliteitstrends zouden continueren, zou IHD veel van zijn belang als oorzaak van voortijdige dood in de nabije toekomst verliezen.

In **Hoofdstuk 5** extrapoleren wij de naar de toekomst de recente trends van mortaliteit van cerebrovasculair accident. In alle landen verminderde het niveau van sterfte aan Cerebrovasculair accident onophoudelijk tussen 1980 en 2005, onder zowel mannen als vrouwen. Indien deze trends zouden continueren, zouden sterftecijfers afnemen met ongeveer de helft tussen 2005 en 2030, met een grotere afname in Frankrijk (ongeveer twee derde) en een kleinere afname in Nederland, Denemarken en Zweden (ongeveer een kwart). Vergelijkbare afnames zouden worden geobserveerd in termen van PGLE. Door bevolkingsvergrijzing zou het absolute aantal gevallen van sterfte aan Cerebrovasculair accident langzaam afnemen in het Verenigd Koninkrijk en Frankrijk en stabiliseren of zelfs toenemen in andere landen.

In **Hoofdstuk 6** onderzoeken wij mogelijke toekomstige trends in mortaliteit van maagkanker tot 2030. Maagkankermortaliteit nam af tussen 1980 en 2005 met ongeveer hetzelfde tempo (3.6-4.9 procent per jaar) voor zowel mannen als vrouwen, en in alle landen. Deze afname is niet afgezwakt in recente jaren en de afname was bovendien niet zwakker in landen met al lagere sterftecijfers in 1980. Indien deze afname zou doorzetten in de toekomst, zouden maagkankersterftecijfers tussen 2005 en 2030 in de meeste populaties met ongeveer 66 procent afnemen. Een twee-derde afname zou ook in termen van PLGE optreden, terwijl het absolute aantal maagkankerdoden met ongeveer 50 procenten zou afnemen. Dus gezien de sterke, stabiele en consequente mortaliteitsafname in recente decennia wordt maagkanker waarschijnlijk steeds minder belangrijk als een doodsoorzaak in West Europa in de komende jaren.

Hoofdstuk 7, vat de resultaten van dit proefschrift samen en bediscussieert de oorzaken van de waargenomen mortaliteitsafname, met bijzonder aandacht voor determinanten in het vroege leven. Ook bespreken wij projecties voor toekomstige jaren. Wij concluderen dat cohortwijze patronen werden gevonden in de daling van mortaliteit, zij het met enkele onregelmatigheden, voor elk van de drie ziekten en in alle landen. Onze bevindingen steunen de verwachting van een realatie tussen veranderingen in vroege levensomstandigheden en veranderingen Cerebrovasculair accident mortaliteit op populatieniveau. Echter, er werd geen sterk bewijs gevonden voor een vergelijkbare relatie met sterfte aan IHD of maagkanker. Indien recente trends in sterfte aan IHD en Cerebrovasculair accident zich zouden voortzetten, zouden deze ziekten veel van hun belang als oorzaak van voortijdige dood in de nabije toekomst verliezen. Hetzelfde geldt, zelfs in sterkere mate, voor maagkanker. Vooral wat betreft IHD en cerebrovasculair accident zal hun incidentie, prevalentie en effect op kwaliteit van leven naar verwachting veel minder afnemen. Dientengevolge zal niet het voorkómen van sterfte, maar het voorkómen van de morbiditeit als gevolg van IHD of cerebrovasculair accident in de toekomst steeds belangrijker worden.

خلاصه پایان نامه

هدف های انجام این پایان نامه ، توصیف روند طولانی مدت مرگ ومیر ناشی از سه بیماری (بیماری احتقانی قلب ، سکته مغزی و سرطان معده) در کشورهای توسعه یافته ، ارزیابی ارتباط بین روند مرگ ومیر این بیماریها وشرایط زندگی در اوایل عمر (که با میزان مرگ کودکان زیر یک سال و تولید ناخالص ملی در سال تولد اندازه گیری گردید) ، و پیش بینی مرگ و میر این بیماریها تا سال 2030 (بر اساس روند مرگ ومیر مشاهده شده از 1980 تا 2005) می باشند.

علت های مرگ اصلی اول و دوم بودن بیماری احتقانی قلب و سکته مغزی ، برخلاف کاهش روند مرگ ومیر آنها در سالیان اخیر ؛ و هم چنین ارتباط احتمالی سرطان معده و شرایط زندگی در اوایل عمر و در نتیجه اثرهای همگروهی محتمل ، دلیل های عمده انتخاب این سه بیماری بودند. به علاوه، به دلیل اشتراک اندک عوامل خطرزای سرطان معده با دو بیماری دیگر, بررسی آن می تواند جنبه های دیگر تاثیر شرایط زندگی اوایل عمربر مرگ را روشن سازد.

ما مرگ و میر حاصله از بیماری احتقانی قلب ، سکته مغزی و سرطان معده را با استفاده از داده های 1950 تا 1999 (برای محاسبات گذشته) و از 1980 تا 2005 (به عنوان مبنای پیش بینی آینده) بررسی نمودیم. برای انجام این کار، ما یک روش تحلیلی آینده نگر طول عمر (با تاکید روی هر دو اثر دوره زمانی و همگروهی) به کار برده ، و مطالعات مقایسه ای را در هفت کشور اروپای غربی ، یعنی : دانمارک، انگلستان و ولز، فنلاند ، فرانسه ، هلند، نروژ و سوئد انجام دادیم.

پنج سری داده به کار برده شد. برای فصل های 2و 3 ، ما سه سری داده استفاده کردیم: اول ، دوم و سوم. داده های **سری اول**، شامل داده های مرگ و میر بیماری احتقانی قلب ، سکته مغزی و سرطان معده و جمعیت در معرض خطر برای دانمارک، انگلستان و ولز، فنلاند ، فرانسه ، هلند، نروژ و سوئد ، بر حسب سال مرگ (1950 تا 1999)، جنس ، و گروه سنی پنج ساله گرد آوری گردید.داده های دانمارک ، فنلاند و نروژ فقط از سال 1951 وداده های سوئد فقط از سال 1952 در دسترس بودند. داده های فرانسه فقط تا سال 1997 و داده های دانمارک فقط تا سال 1998 قابل دست یابی بودند.این داده ها از دفترهای ملی آمار و ارگانهای مربوطه جمع آوری گردید. برای به دست آوردن داده های **سری دوم**، داده های مرگ ومیر کودکان زیر یکسال،(بنا به تعریف : تعداد موارد مرگ در سال اول زندگی در 1000 تولد زنده) برای دوره زمانی 1969-1860 استفاده گردید. **سری سوم** شامل داده های تولید ناخالص ملی می باشد.برای ارزیابی روندها ی واقعی تولید ناخالص ملی ، یعنی تولید ناخالص ملی محاسبه شده بر مبنای قیمت های ثابت 1995 بر حسب میلیون واحد پول ملی ، بین 1865 و 1939 ، داده های ملی در زمانهای گذشته به کار برده شد. برای هلند ، این اطلاعات تاریخی فقط از سال 1900 به بعد دردسترس بود، وداده های سالهای قبل از مرکز آمار هلند گرفته شد.برای فصل های 4 تا 6 ، از **سری چهارم** داده ها استفاده گردید. داده های مرگ (تعداد مرگ و جمعیت در معرض خطر بر حسب جنس و گروههای سنی پنج ساله) حاصله از بیماری احتقانی قلب ، سکته مغزی و سرطان معده برای دانمارک (نه برای سکته مغزی در فصل 5)، فنلاند ، فرانسه، هلند ، نروژ ، سوئد، و بریتانیای کبیر، برای سالهای 1980 تا 2005 از Eurostat (دانمارک از 1999 تا 2001 ، فرانسه از 1998 تا 2005)به دست آمد. و بالاخره ، **سری پنجم** داده ها، شامل تعداد پیش بینی شد ه جمعیت آینده برای همه کشورها به جز نروژ از Eurostat (سناریوی پایه) به دست آمد و داده های نروژ از مرکز آمار نروژ (سناریوی رشد متوسط ملی) گرفته شد.

بخش اول پایان نامه، یعنی فصل های 2 و 3، روندهای گذشته مرگ حاصله از بیماری احتقانی قلب ، سکته مغزی و سرطان معده را در هفت کشور اروپائی توصیف می نماید. در این فصل ها ، نقش اثرهای گذشت زمان و همگروهی بر روندهای مشاهده شده مرگ بین سال های 1950 و 1999 مورد بررسی قرار گرفت. به علاوه، ما نقش عوامل محیطی و شرایط زندگی اوایل زندگی (اندازه گیری شده با میزان مرگ و میر کودکان زیر یکسال و تولید ناخالص ملی در سال تولد) روی روندهای مرگ اختصاصی –همگروه بیماری احتقانی قلب ، سکته مغزی و سرطان معده را تخمین زدیم.

فصل2 روند مرگ ومیر حاصله از بیماری احتقانی قلب و سکته مغزی را در رابطه با مرگ و میر کودکان زیر یکسال توصیف می نماید. ما دریافتیم که مرگ ناشی از بیماری احتقانی قلب تا همگروه تولد 1900 افزایش یافته ولی از این سال شروع به کاهش نموده است؛در حالیکه سطوح مرگ ناشی از سکته مغزی تاهمگروه تولد 1880 ثابت بوده ، ولی از این سال به بعد سریعا کاهش یافته است. یک رابطه مثبت قوی بین سطوح اختصاصی-همگروه میزان مرگ کودکان زیر یکسال و میزانهای مرگ سکته قلبی (ولی نه برای بیماری احتقانی قلب) یافت شد.این نتایج ، سایر مطالعات نمایانگر ارتباط بین شرایط زیست در اوایل زندگی ومرگ ناشی از سکته مغزی را ، حتی در سطح ملی حمایت می کند وبا آنها همخوانی دارد.مطالعات آینده باید مشارکت اختصاصی عوامل اوایل زندگی و کاهش های اخیر مرگ ومیر ناشی از بیماری احتقانی قلب وسکته مغزی را تبیین نمایند.

در **فصل3**، ما ارتباط روند دوره ای مرگ از سرطان معده را با روند میزان مرگ کودکان زیر یک سال و تولید ناخالص ملی در سال تولد بررسی نمودیم. نتایج ما ، اختلاف های عمده ای را بین همگروه های تولد از نظر مرگ ومیر سرطان معده نشان داد.در هر کشور، این اختلافات همگروهی رابطه نزدیکی با سطوح میزان مرگ کودکان زیر یک سال و تولید ناخالص ملی در سال تولدداشت. ولی ارتبا ط های قویتر با شرایط زندگی در سنین بالاتر مشاهده شد.در مقایسه بین کشورها ، میزانهای مرگ از سرطان معده رابطه استواری با سطوح ملی میزان مرگ کودکان زیر یک سال و تولید ناخالص ملی در سال تولد نداشتند.در نتیجه، به نظر می رسد که شرایط زندگی در اوایل زندگی تاثیر عمده ای بر روند دوره ای مرگ سرطان معده نداشته باشد.کاهش مرگ ومیر احتمالا مرتبط با عوامل اختصاصی تری مثل کاهش شیوع هلیکو باکتر پیلوری می باشد.

در **بخش دوم** پایان نامه، فصل های 4 تا 6، روند های آینده مرگ از بیماریهای ذکرشده بالا تا سال 2030، بر اساس روندهای مرگ مشاهده شده بین 1980 و 2005 در هفت کشور اروپائی ، پیش بینی شده اند.میزان های مرگ ومیر، تعداد مرگ ، و سال های بالقوه از دست رفته پیش بینی شده برای سال 2030 با ارقام مشابه در سال 2005 مقایسه شده اند.

فصل 4 کاهش های احتمالی در مرگ ومیر ناشی از بیماری احتقانی قلب در هفت کشور اروپائی را تا سال 2030 شرح می دهد.در کلیه کشورها ، میزان های مرگ از بیماری احتقانی قلب در هر دو جنس از 1980 تا 2005 به طور پیوسته کاهش داشته است.میزان های مرگ تطبیق شده سنی در سال 2030 (در مقایسه با سال 2005)تا حدود 50%کاهش می یابد، اگرروند های گذشته ادامه یابند. تاثیر بیماری احتقانی قلب روی امید به زندگی در بدو تولد در اکثر جمعیت ها تا حدود 25 تا 50 در صد کاهش می یابد.به علت افزایش جمعیت سالمندان، تعداد مرگ از بیماری احتقانی قلب روند کاهشی آهسته و یا حتی افزایشی خواهد داشت.در نتیجه، اگر روند کنونی مرگ از بیماری احتقانی قلب ادامه یابد، در آینده ای نزدیک ، بیماری احتقانی قلب بخش عمده اهمیتش را به عنوان یک علت اصلی در مرگ زودرس از دست خواهد داد.

در **فصل 5**، ما روند آینده مرک را برای سکته مغزی پیش بینی نمودیم. در همه کشورها و در هر دو جنس، میزان های مرگ از سکته مغزی به طور پیوسته تا سال 2005 کاهش داشته است. اگر این روندها ادامه یابند، میزانهای مرگ تطبیق شده سنی در سال 2030 به میزان نصف میزان های سال 2005 خواهند رسید، با کاهش های بیشتر در فرانسه (در حدود دو سوم)، وکاهش های کمتر در هلند ، دانمارک و سوئد(در حدود یک چهارم).میزان های کاهش مشابهی برای سالهای بالقوه از دست رفته وجود خواهد داشت. به علت افزایش جمعیت ، تعداد مرگ سکته مغزی کاهشی آهسته در بریتانیای کبیروفرانسه ، ثابت و یا حتی افزاینده در سایر کشورها خواهد داشت.

در **فصل 6**، ما روند های مرگ سرطان معده را تا سال 2030 پیش بینی کرده ایم. میزان های مرگ ازسرطان معده درهمه کشورها و هر دو جنس از 1980 تا 2005 ثابت (حدود 4.9-3.6 درصد در سال) بوده است.میزان کاهش در سالهای اخیر متوقف نشده و در کشورهای با میزان های مرگ پائین تر در 1980، کوچکتر نیست.اگر این کاهش در آینده نیز ادامه یابد، میزانهای مرگ سرطان معده در اغلب جامعه ها ، بین 2005 و 2030، تا حدود 66 درصد کاهش می یابد.سالهای بالقوه از دست رفته کاهشی حدود دو سوم خواهد داشت، در حالیکه تعداد مرگ تا 50 در صد کاهش می یابد.بنا بر این ، از نظر کاهش های مرگ ومیر قوی ، ثابت و استوار در سال های اخیر، سرطان معده احتمالا به طور روز افزونی در آینده، اهمیت کمتری به عنوان عامل مرگ در اروپا خواهد داشت .

فصل 7، نتایج اصلی را خلاصه می کند و عوامل مولد کاهش مرگ ومیر در اوایل زندگی در گذشته و پیش بینی های احتمالی در سال هایپیش رو را بررسی می نماید.ما نتیجه گرفتیم که الگوهای کاهش همگروهی یافته شد، که ناهمگونی هائی در طول زمان برای هر سه بیماری ودر همه کشورها داشت. یافته های ما، انتظار ارتباط بین تغییر شرایط زیست اوایل زندگی و تغییرات سطوح جمعیتی سکته مغزی را حمایت می کنند. ولی، هیچ گونه شواهدی برای مرگ از بیماری احتقانی قلب یا سرطان معده مشاهده نشد. ، اگر روند کنونی مرگ از بیماری احتقانی قلب و سکته مغزی (همچنین سرطان معده) ادامه یابد، در آینده ای نزدیک این بیماریها بخش عمده اهمیتشان را به عنوان علتهای اصلی در مرگ زودرس از دست خواهد داد.به ویژه برای بیماری احتقانی قلب و سکته مغزی، تاثیر بروز و ناتوانی آنها ممکن است کاهش کمتری داشته باشد. در نتیجه، پیشگیری بیماری احتقانی قلب و سکته مغزدرآینده به طور روزافزونی،متکی بر ناتوانی وابسته به بیماری است تا به جای مرگ ومیر.

Appendix

Causal mechanisms/trends in factors

The factors underlying the favourable mortality trends are variable and multifactorial. They can be explained by primary [1] and secondary [2] preventions with widely variation from country to country [3]. In addition, many interactions occur among these factors, and for each one of the factors a network of determinants is established or proposed in varying degree of detail. In this appendix, after explaining of the potential causal mechanisms behind the mortality trends from IHD, stroke and stomach cancer, the analysis on contribution of three important risk factors (i.e., smoking, hypercholesterolemia, and hypertension) on stroke mortality decline in Finland will be presented.

A.1. Potential causal mechanisms

A.1.1. IHD and stroke

These two diseases have many common risk factors, with possible various effects on diseases, differ in the strength and even direction of association [4], and many of them widely accepted as being causal [5].

Population differences in mortality from IHD and stroke are generally well documented in the report of WHO MONICA Project [6], which showed that two thirds of the decline in IHD and stroke mortality remains unexplained even after control for classical risk factors [7]. A part of the unexplained trends might be due to changes in other risk factors, such as socioeconomic status, food consumption, or different combinations of some or all of these [7]. Early life exposures might also be one of the other factors that contribute to trends in IHD and stroke mortality [8]. In addition, findings from INTERHEART study suggested that nine modifiable risk factors explain most of the risk worldwide [9]. Moreover, INTERSTROKE study suggested that ten risk factors are associated with 90% of the risk of stroke, especially blood pressure, smoking, physical inactivity, and diet [10].

There are many determinants which could explain mortality trends of IHD and stroke such as:

Age and gender: Each of these two factors serves as a marker for underlying behaviors, exposures, or other factors (cofactors) more directly related to disease risks and outcomes. In addition, they have two important aspects in common. The first aspect is that they are dimensions of diversity among populations, revealing health patterns- demonstrated variations in the distribution of disease or health-related conditions within or between populations- that may

be of public health importance. The second aspect is the presumption that each of them is 'unmodifiable', in contrast to such factors as dietary patterns, which are clearly responsive to intervention. However, association of any of these two factors with disease rates or risks may also reflect underlying environmental factors related to social conditions, behavioral patterns, specific exposures, or other characteristics. For example, increasing blood pressure in adulthood was long regarded as a natural or inevitable concomitant of aging.

Age: The important effect of age in mortality from IHD and stroke can be summarized in four main aspects:

1) The effect of age throughout the life span, from determination of genetic makeup and the course of fetal development to the ages of IHD and stroke. With respect to stages of life, it is necessary to note the importance of distinguishing between a true effect of childhood (fetal and neonatal) factors and factors in adulthood in determining risks of adult cardiovascular diseases [11].

2) There are different population patterns of change in blood pressure with age. In most populations, blood pressure does increase with age in adulthood; thus, if two populations were compared regarding the prevalence of high blood pressure, a finding of a higher prevalence in the population with the greater proportion of older adults would be uninformative. Therefore, age-specific comparisons are more informative than crude comparisons, which do not take age into account.

3) Morbidity and mortality data in the elderly differ from those for younger adult age groups in two respects. First, data on specific diagnoses and causes of death may be less reliable for older individuals. Second, the high prevalence of many cardiovascular disease risk factors in older persons tends to result in reduced estimates of *relative* risk for cardiovascular events or conditions, because even those who remain clinically free of these conditions are at greater risk than younger persons.

4) Older age is still the most important risk factor for stroke [12]. The potential relationships between older age and stroke include being a major cause of morbidity and mortality in an aging population [13], increasing the incidence rate of stroke exponentially with advancing age [12], and rising of the mean age of the stroke patients reflecting the increasing number of elderly persons in the population [14, 15].

Gender: Discussion of differences by gender in the natural history of atherosclerotic and hypertensive diseases has focused on women and the disparities between their experience and that of men [16]. This emphasis reflects in large part a sense of relative neglect of the problem of cardiovascular disease in women, for whom its cumulative lifelong burden is actually no less than that for men.

There are many sex differences in risk factors including lower mean value of systolic and diastolic blood pressure and total cholesterol concentration (beginning in adolescence) but greater prevalence of physical inactivity and overweight [17], and smoking behavior [17]. Plausible bases for such effects include chromosomal, endocrinologic, or reproductive factors could be interpreted variously as evidence of biologic, social, cultural, or behavioral effects. There are also different patterns of activity, occupation, interpersonal relationships, exposure, and access to education, health information or health services. Access to long-term programs supporting risk factor assessment and management may also present different opportunities for women and men; for example, women received fewer prescriptions for post-hospital treatment [18] or received coronary angiography less often than men [19].

High blood pressure: Blood pressure varies throughout the life span, and the distribution of blood pressure may vary over time within a population. Furthermore, the death rate of a population is determined in a significant part by its blood pressure distribution [20, 21]. The risks specifically for IHD and stroke are related to blood pressure levels [22]; which is explained well in MONICA Project [23]. Blood pressure is also a substantial factor in differential risks of these events, especially stroke, within populations; and interventions to control high blood pressure in whole communities or treat individuals to reduce or prevent high blood pressure have been shown to be effective [21].

Collins and Peto remarked that the reduction in stroke events by treatment matches the prediction from the attributable risk of stroke due to blood pressure; however, for coronary events, only about two-thirds of the predicted treatment effect was found [24]. They argued that stroke may reflect more immediate blood pressure effects that respond to treatment rapidly, whereas IHD may require longer time to exhibit the full benefit of blood pressure reduction. Casper et al discussed on the assumption that improved treatment of hypertension is the primary determinant of the decline in stroke deaths [25]. Their analysis suggested that the trends for hypertension treatment or control and for stroke mortality rates were parallel over the longer periods, not within shorter periods. They concluded that mass drug treatment of hypertension cannot bring about the 'optimal decline' in stroke mortality, and suggested that cultural change was more relevant than medical management to hypertension prevention. They posed a socio-cultural hypothesis of the population causes of mass hypertension. In another study, Jacobs et al concluded that 1) the stroke mortality rate changes since 1960 have followed population blood pressure changes, influenced to some extent by the expanded use of antihypertensive medication, and 2) the full potential of this use in the population may not yet have been reached [26].

Finally, other life-style factors have also probably influenced the decline of stroke deaths, both directly (e.g., the decreasing prevalence of cigarette smoking)

and indirectly (e.g., the effects of decreased sodium and alcohol intake on blood pressure).

Blood lipid: It is clear that age-specific death rates from IHD have declined while decreases have occurred in mean total cholesterol concentration [27], with a significant variation between age patterns of cholesterol concentration among populations [28]. The relation between dietary fat and cholesterol intake and blood cholesterol concentration has also been quantified [29].

Increases of cholesterol with age in men are apparent from the 20s to the 40s or beyond reflecting differences in lifetime history of the different age groups (cohort effects); for women, their age curve for total cholesterol concentration also fell at the oldest ages, like that for men, but with a peak in the curve at ages about 15 years older [28]. In addition, the inverse relation of the concentration of high-density lipoprotein (HDL) cholesterol (popularly, the "good" cholesterol) to risk of IHD has been reported [30]. It has been suggested that while in general both low-density lipoprotein (LDL) and HDL cholesterol relate to coronary risk in women as in men, the inverse risk gradient for HDL cholesterol is stronger for women and that LDL cholesterol of a given level may be less atherogenic for women [31]. The implication of HDL cholesterol as having an independent and inverse relation to risk of IHD has long antecedents, as early as 1951, as reviewed in previous studies on IHD in different populations [32].

Smoking: Unless the epidemic of cigarette smoking is controlled in developed countries [33], this may constitute the risk factor of the 21st century as well, especially for cardiovascular diseases [20]. The reduction in prevalence trends of cigarette smoking in the population during the last decades imply large changes in the frequency of exposure to tobacco smoke [34]; however, it is clear that cigarette smoking alone does not indicate the full extent of tobacco exposure in the population, especially among youth, although pipe and cigar smoking are generally much less prevalent than cigarette smoking.

In addition, there is a relationship between smoking and two other major risk factors, i.e., blood pressure and cholesterol concentration, for IHD mortality [35], and has interact with these risk factors in the development of atherosclerosis during adolescent and young adulthood [36]. Therefore, these three major cardiovascular disease risk factors are closely interrelated and it is important that they be considered together and not in isolation.

Furthermore, exposure to tobacco smoke is associated with several factors specifically relevant to cardiovascular diseases, including lipid abnormalities such as increased LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglyceride and decreased HDL cholesterol, and increased blood pressure [34]. The personal habit of cigarette smoking is most important for the occurrence of cardiovascular diseases due to its very high prevalence in many populations [33], with focus on the initiation of smoking mostly in childhood and

adolescence. Other important conditions of progression in smoking behavior are socioeconomic, environmental, behavioral, and personal factors as well as the role and tactics of the tobacco industry.

Moreover, exposure to smoked tobacco occurs passively when nonsmoking persons share the environment of smokers; this form of exposure underlies studies of the effects of environmental tobacco smoke (ETS). For smokers, there is also often additional exposure to smoke generated by others. In addition, smokeless tobacco, commonly used by younger population, is toxic due to constituents of tobacco juices, even without tobacco's combustion products; its use may result in higher nicotine due to the acidity of saliva and its prolonged contact with the tobacco [34].

Genetic factors: Although genetic testing for certain of the lipid disorders is potentially applicable at birth for those with known family histories of such conditions, few if any recommendations for neonatal testing are proposed. Rather, family history is emphasized as a means of predicting increased risk for individual children and adolescents. Because parents and even grandparents of young children may not yet have reached the peak ages at risk of the risk factors themselves of for major cardiovascular events, updating the family history is needed and could then lead to more specific investigation if warranted.

Furthermore, specific genetic determinants of risk could potentially be evaluated once an individual was found, for example, to have an elevated cholesterol concentration. A concern is that genetic heterogeneity of populations may be emphasized to such a degree that general recommendations lose acceptance in favor of individualization of all interventions, perhaps requiring genotyping before action is taken on behalf of any individual [37]. Unless, such strategies became feasible on a very broad scale, great caution would be indicated in considering the implications for public health of dismantling population-wide recommendations.

Family history: The family unit is important for prevention of the risk factors in the first place, in keeping with the cardiovascular prevention schedule. Family history has been championed as a key to identification of the coronary-prone family [38]. Persons or families to be at high risk may in principle be defined in four categories: those presently free of risk factors but especially likely to develop major risk factors in the future; those with established risk factors; those already experiencing acute cardiovascular disease events; or those surviving such events or otherwise recognized as having clinically detectable disease. With the possible exception of the first of these categories, recognition of high risk occurs mainly in the context of health care setting or in screening programs, which ideally provide referral for health care. Therefore, policies concerning high risk are closely related to aspects of clinical practice.

Diet: From a population perspective, there are many determinants of dietary behavior that influence the ultimate nutritional status of individuals. It should be noted that diet is complex, comprising countless specific nutrients, food sources, variations in preparation, and combinations of these. Within any population, there may be wide differences in typical dietary habits of individuals, and within individuals, diet may be highly variable from day to day or between periods of life. The diet of the individual in turn is strongly, and in some circumstances completely, determined by external factors of which he or she is hardly conscious. Even the choice of foods, the timing, and the company of others for a given meal may be largely passive or automatic, on a day-to-day basis. Diet can be described in various ways- in reference to specific nutrients, in terms of foods, and in terms of quality of dietary composition.

In addition, the ascendancy of fat and sugar and the decrease in flour and fiber, and the very recent sharp increase in animal protein and fat through an unprecedented pattern of meat and milk consumption could demonstrate marked rates of dietary change. In addition, changes in food technology have brought about even more-accelerated dietary change in the most recent decades.

Furthermore, dietary assessment of individuals or populations poses many difficulties; for example, there are several concepts of diet within and/or between populations, and one or more of these may be relevant to a particular question or investigation. However, despite these methodological difficulties in population studies of diet, extensive observations documenting adverse effects of the recent dietary patterns exist; especially for total and saturated fats, specific fatty acids, cholesterol, fiber, and salt [39]. Moreover, it is clear that dietary patterns can be modified, at both population and individual levels [40]. There is consistency in the general recommendations for prevention or reversal of dietary habits, by official international and national health agencies, to limit intakes of fats, saturated fats, and salt and to increase intake of fruits, vegetables, and legumes to maintain a balance between total energy intake and energy requirements [40].

Physical inactivity: Mechanisms that either increase myocardial oxygen supply or decrease myocardial work and oxygen demand are emphasized, suggesting that the principle effects of physical activity on the heart would tend to reduce the risk of myocardial ischemia or decrease its severity, especially under circumstances of increases workload or diminished blood flow. Physical inactivity also affects many other aspects of physiology, metabolism, and psychology [41]. The mechanisms by which physical activity could influence measures of occurrence of cardiovascular diseases are their effects on reduced risks of obesity and undesirable body fat distribution, adverse blood lipid profile, and high blood pressure [42, 43].

Within populations, variation in risk of cardiovascular diseases in relation to physical inactivity, other levels of activity, and physical fitness has been reported from numerous studies [44]. In addition, one of the important dimensions

of physical inactivity includes the distinction between occupational (work) activity and non-occupational or leisure time physical inactivity. Early studies, through the 1970s, focused on occupational activity, while more recent ones have emphasized non-occupational activity [45].

Interventions to influence physical activity in populations can potentially affect both the incidence and the prevalence of physical inactivity; i.e., in short-term, its prevalence could be reduced only by measures bringing about change to a physically active state for a substantial proportion of the population who are currently physically inactive [44]. Reducing incidence of physical inactivity requires measures to establish non-sedentary habits early in life and maintain them. As a long-term result, prevalence of inactivity in adulthood would also thereby be reduced.

Obesity and overweight: The risks of cardiovascular diseases that may be increased directly or indirectly through obesity are prominent health concerns. The question of whether population differences in rates of atherosclerotic and hypertensive diseases mortality are attributable to obesity has been addressed in few studies [46]. At the population level, obesity may refer to the prevalence of a specified level of body mass index (BMI), waist-hip ratio (WHR), sum of skinfold thickness as measured at selected body sites, or some other measures [47]. Furthermore, overweight connotes a relative excess of weight. One further aspect concerns the percent body fat changes markedly during infancy and childhood, compared to essentially constant body fat in adulthood [48]. Furthermore, secular trends toward increasing prevalence of obesity have been occurring also in childhood; and there is little disagreement that childhood obesity is a significant health concern in the population [49]; thus, the evidence of increasing mean values of BMI in the adult population suggests the importance of preventive measures at earlier ages [50]. The population-wide measures advocated for improvement of dietary patterns and reduction of physical inactivity are the principal means proposed for prevention of obesity at the population level. In many countries, the secular trend toward increasing prevalence of obesity is evidence of failure of population-wide strategies against this disorder.

Diabetes mellitus: Although the relation of diabetes or categories of baseline blood glucose levels and risk of IHD has illustrated before [51]; however, the complex of blood glucose, insulin, and diabetes has not been examined for its possible role in explaining variation in coronary death rates among different populations [36]. While blood insulin concentration is itself a risk factor for IHD has been studied with respect to both endogenous insulin (hyperinsulinemia or insulin resistance) and exogenous insulin (insulin therapy), the studies of both aspects can be described as inconsistent and the role of insulin as a heart disease risk factor remains controversial [52]. Association between diabetes and stroke has also been demonstrated [53], and it is a potentially modifiable factor of stroke [54].

Therefore, because the presence of diabetes increases the risk of IHD and stroke, emphasis has increased on the prevention of cardiovascular conditions as an important component of care in diabetes [55]. Public health concern has therefore expanded to include a wider spectrum of disturbances of this regulatory complex.

Moreover, non-insulin-dependent diabetes mellitus (NIDDM) and insulin resistance together are the most relevant aspects of diabetes for risks of atherosclerosis and hypertension in the population [56]. Population studies have suggested a number of predisposing factors for diabetes such as physical inactivity, systolic blood pressure, high-density lipoprotein (HDL) cholesterol, smoking, and IHD [57]. Other factors may also participate in the increased atherogenesis of insulin resistance and diabetes such as elevated blood concentrations of glucose, triglyceride, and fibrinogen; association of risk factors such as obesity, hypertension, and adverse blood lipid profiles with elevated insulin concentrations also is evident in early adulthood and even in childhood [58].

Socio-economic status (SES): Although SES has been found to be associated with cardiovascular diseases, with a changing patterns over time [59], the declines in cardiovascular mortality have not affected all socioeconomic groups equally, and several cardiovascular risk factors are also inversely associated with socioeconomic status [59]. SES generally constitute "fundamental causes" of disease, not merely markers of true causes or pointers toward risk factors that operate more proximally in relation to disease [60].

Among the commoner changes in social conditions taking place in recent decades, and presumably to continue, are changes in culture, lifestyle, and environment attendant on economic development, migration, or both [61]. Furthermore, cultural change is a very important part of social condition [62]. Factors such as urban residence, white-collar occupation, and geographic and occupational mobility are the most considerable factors; and their associations with cardiovascular diseases were independent of diet, relative body weight, blood pressure, smoking, and parental longevity [62], as well as education and some aspects of the origin of cardiovascular disease in childhood or adolescence [63], and social class, operating through variation in lifestyles, and specific exposures to produce differences in health [64].

Low SES is marked by higher risks of many diseases and adverse health conditions such as atherosclerosis and hypertensive diseases. There is an overlap between concentration of cardiovascular risk factors and lower SES. The important issues in this regard include factors such as lower levels of literacy or education, less likelihood of employment, and more limited access to health care sources.

Personal characteristics: There are many factors which could be addressed in this regard such as: psychosocial patterns, pro- and anti- oxidants, and homocysteine.

Psychosocial Patterns: Adverse psychosocial patterns may be considered influential for causation of atherosclerotic and hypertensive diseases or for limiting the effectiveness of preventive measures [65]. Conversely, favorable behavior patterns that occur spontaneously or as a result of health education, counseling, or other interventions are expected to reduce risks and to reinforce preventive strategies by favorable effects on patterns of diet, physical activity, medication adherence, and other such behaviors. The areas most extensively or recently investigated are Type A behavior pattern, occupational stress, and social support [66]. These personal characteristics are primarily psychosocial rather than metabolic or physiological in nature.

Pro- and Anti-oxidants: A metabolic mechanism has been proposed that strongly influences the behavior of LDL molecule and potentates its role in atherosclerosis [67]; in addition, the distinction between dietary and supplementary intake of the antioxidants (such as vitamins A, C, and E) is important to interpretation of evidence. It is apparent that the various antioxidants differ in important respects in their relative potency and behavior as protective agents against LDL oxidation; and from this perspective, vitamin E and beta-carotene might be expected to have greatest potential benefit [68]. If the action of antioxidants protects against transformation of LDL to an especially virulent promoter of atherosclerosis, antioxidants would be opposed by any factor whose action favors production of O-LDL, such as certain metals (like iron or copper) or their compounds, in which act as a pro-oxidant. Research has shown a role of excess dietary iron in increasing the risk of acute myocardial infarction in men and possibly postmenopausal women, explaining variation in the relation of LDL cholesterol to risk of IHD in some populations and suggesting that dietary guidelines should cautious against excessive iron intake [69].

Homocysteine: Homocysteine is an amino acid in blood which its too much concentration in blood is related with increasing risk of IHD and stroke [70]. There is a close link between homocysteine metabolism and the B vitamins in that either a pyridoxal phosphate-dependent enzymatic reaction or a transfer of methyl groups from vitamin B_{12} or folic acid is required to convert homocysteine to its immediate metabolic products [71]. In addition, based on the estimated frequency of increased homocysteine concentration in the general population, it was concluded that 10% of the population risk of IHD was attributable to this factor [72]. There is also a possibility that the potential reduction in IHD rates by increased folic acid intake, under the assumption that the reduction of homocysteine concentration known to result from folate administration, would reduce disease rates [72]. Meanwhile, there is a strong argument that consideration of increased folate intake is a potential intervention to reduce the risk for IHD [73].

A.1.2. Stomach cancer

Some of our results suggest that secular trends in stomach cancer are largely determined by changes in adult socioeconomic circumstances and lifestyles, rather than childhood [74]. For example, the marked cohort pattern of stomach cancer mortality, which peaked among birth cohorts born around 1875, might be determined by cohort-specific trends in smoking, alcohol consumption and other factors related to later phases of the life course. Similarly, improvements during the 20th century in environment and nutrition may have resulted in a gradually lower incidence of stomach cancer, while more accessible and effective facilities for cancer therapy may have helped to reduce its case fatality [74].

Stomach cancer rates throughout the world vary widely, implying that other factors are also important in its development [75], maybe because of the differences in gastritis patterns related to *H. pylori* [75]. It affects by producing an environment conductive to carcinogenesis, interacting with other lifestyle and environmental exposures [76]. Furthermore, there is a strong association between *H. pylori*-associated gastritis and stomach cancer [77]; and many epidemiological studies indicate that *H. pylori* infection plays an important role in stomach carcinogenesis by inducing chronic inflammation in the gastric mucosa [77]. *H. pylori* might affect through facilitating the growth of nitrosating bacteria [78] or inhibiting gastric secretion of ascorbic acid [79], and by interacting with other factors, including dietary habits, host factors, and the virulence of the infection [80].

H. pylori infection is a more important contributor of the observed mortality trends from stomach cancer, supported by previous epidemiological studies [77]; however, *H. Pylori* would account only for half of the world total for stomach cancer by a probably synergistic or antagonistic role of dietary and other exogenous factors [81]. Furthermore, evidence suggests that *H. pylori* infection mainly acquired during early childhood, and infection persists throughout the life [75] reflecting the effects of environmental and lifestyle risk factors [82] such as the shared bed in childhood, lack of fixed hot water supply, lower educational attainment [75], low income, poor education and low living conditions during childhood such as poor sanitation and overcrowding [83]. Chronic *H. pylori* infection is also associated with stomach cancer [84]; therefore, control of this infection would reduce the occurrence of chronic gastritis and peptic ulcer and might substantially lower the risk of stomach cancer [85]. In fact, treatment of *H pylori* infection is an appropriate target for prevention of stomach cancer [84], and by eradicating *H pylori*, gastric inflammation can be cured [77]. Although, control of the *H. pylori* infection might substantially reduce the risk of stomach cancer [85]; however, among several therapeutic regimens to cure *H. pylori* infection [75], none of them is able to cure *H. pylori* infection 100% [86], and the medication combinations were able to cure *H. pylori* infection in more than 85% of the patients [86]. In addition, further improvement with regards to life style might

occur, and therefore, other risk factors may become more important, including dietary factors.

Treatment is expected to play some role [87], and changes in diagnosis and treatment may have made a contribution to the declining incidence and mortality rates of stomach cancer [88, 89]. Factors are related to treatment and general management of patient is also expected to explain the residual variability in survival between European countries [87]. These factors include greater operative experience leading to more skilled surgeons, earlier diagnosis and different biology of stomach cancer between countries [90]. Since the appropriate treatment is mainly surgical [91], the proportion of patients underlying surgical intervention is the factor most likely to help further interpretation of differences among countries [87]. Thus, the surgical workload associated with stomach cancer is not declining [92]; this is because the incidence has remained almost static, which may be due to the relative increase in the numbers of older people in the population, who are at greater risk of developing stomach cancer [92]. Incidence and workload should determine resources allocated to this disease rather than mortality statistics [92]. Treatment costs are strongly related to age, cancer type and stage of disease at diagnosis [93]. The costs of surveillance and monitoring activities needed in the intermediate phase are much lower than costs for first and terminal treatment but, as they may continue for a long period of time, their impact on the total cost of cancer care is not negligible [94].

A.2. The contribution of risk factors on stroke mortality in Finland

A number of risk factors have associations with stroke mortality [4]. Epidemiological studies showed that two thirds of the fall in mortality from stroke in men and half in women can be explained by changes in the three main risk factors, i.e., smoking, hypertension, and total cholesterol [95]. It might be because of the fact that modification of classic risk factors in the population can affect the rates of stroke [96]. Indeed, early declines in stroke mortality are due to changes in diet and lifestyle factors, while the more recent declines are due to improvements in modern cardiovascular treatment [97]. It should also be noted that attributing past falls in stroke mortality to risk factor changes or effective medical interventions is difficult because favourable trends in both have occurred simultaneously.

In order to reveal how important it would be to continue the achievements of primary prevention (as compared to curative care), the attributable effects of the contribution of main risk factors (i.e., smoking, hypercholesterolemia, and hypertension) on stroke mortality trends in Finland have been assessed.

To take into account the attributable effects to the contribution of main risk factors (smoking, hypercholesterolemia, and hypertension) in Finland, the previous research were considered for both genders; i.e., smoking (8.8%), high

cholesterol (37%), high blood pressure (7.5%), three risk factors combined (53.3%), and treatment (23.1%) on stroke mortality decline [98].

To cover the potential possibilities, the following scenarios have been formulated including reference scenario (continuation of the past trends), smoking scenario (take into account only the effect of elimination of smoking), high blood pressure scenario (take into account only the effect of prevention of high blood pressure), high cholesterol scenario (take into account only the effect of elimination of high cholesterol), treatment scenario (take into account the effect of treatment), and finally three risk factors scenario (take into account the effects of these three risk factors combined).

In table A.1., the projected mortality rates in 2030 in different scenarios have been compared to the rates in 2005. In this table, the contribution percentages of main risk factors (i.e., smoking, high cholesterol, and high blood pressure), as well as a combined contribution of these three risk factors, in mortality declines for both genders were compared with reference scenario (i.e., the observed mortality declines). The removal of the effects of high cholesterol in the population are substantially more effective than the removal of smoking or high blood pressure alone, even more effective than treatment alone, in both men and women. These effects would be even more effective when combining the effects of eliminating of these three risk factors altogether. However, even with combined effect, reference scenario shows more decline in all countries and for both genders, mainly because of the effect of other factors like unexplained factors.

Table A.1- Age standardized stroke mortality rates (per 100 000) in Finland, projections by sex and scenario from 2005 to 2030

Scenario[$]	Year	Men	Women
	2005	64.72	94.51
Reference	2030	29.32	42.52
	2030/2005[*]	0.45	0.45
No Smoking	2030	31.78	46.31
Contribution	2030/2005	0.49	0.49
No high BP	2030	31.41	45.73
Contribution	2030/2005	0.49	0.48
No high CHL	2030	41.11	60.79
Contribution	2030/2005	0.64	0.64
No risk factors	2030	47.65	71.08
Contribution	2030/2005	0.74	0.75
No treatment	2030	36.22	53.18
Contribution	2030/2005	0.56	0.56

*. The figure of 2030 divided by the related figure in 2005.

$. The contribution percentages of main risk factors in mortality decline for both genders are: smoking 8.8%, high cholesterol 37%, high blood pressure 7.5%, three risk factors combined 53.3%, and treatment 23.1% [98].

The changes in stroke mortality may be due to changes in disease incidence rate [99]. While some studies have shown stable incidence rates of stroke [15] (such as Sweden [100]), other studies reported a continuing declining trend in incidence of stroke in western countries [101], Norway [102], Finland [103] and Sweden [104] through the 1970s and the early 1980s; but in the late 1980s and early 1990s this trend seemed to have come to end, and increased [101]. During the first decade of the 21st century incidence trends have also been declining (Finland [105]), or were stable (France [106]). While declining incidence rates were explained mainly by cigarette smoking [107], stable stroke incidence rates could be related to control of risk factors [108]. Meanwhile, the increasing incidence rates were explained by unfavourable changes in risk factor profile [107].

Looking at the observed trends in the past, the decline in mortality from stroke will continue in the future, which supports by other studies [109]. It might be explained by two facts. First, there is a highly consistency in the recent trends in stroke mortality in western Europe [110]. Our findings also showed that the declines had persisted up to recent years in these six populations. Second, the cohort patterns of declines are also very important. In our previous study, we have already confirmed the well-known cohort-wise decline in stroke mortality over time in these European countries [111]. We have also discussed about the effects of living conditions in childhood before [111].

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Curriculum Vitae

Masoud Amiri was born on the 11th of February 1966 in Isfahan, Iran. He started studying Public Health at Isfahan University in 1983. After his B.Sc. in Public Health in 1987, he continued his study in Epidemiology at Shiraz University of Medical Sciences. During his study at Shiraz, he was teaching at different universities such as Shiraz, Isfahan, and Bushehr Universities. After obtaining his degree of Master of Science in 1991, he has started teaching in Shahrekord University of Medical Sciences as academic staff. He has taught epidemiology, public health, biostatistics, research methodology, and SPSS. He has headed the students' research methodology workshops of the university from 1991 to 2002. In 1999, he has started to collaborate with Isfahan Cardiovascular Research Center (ICRC) as epidemiologist. In 2001, he was granted a scholarship to continue his study. He came to Rotterdam in Nov. 2002. He obtained his M.Sc. and D.Sc. in Epidemiology at Department of Public Health in Erasmus Medical Center, Rotterdam in 2003 and 2005 respectively. He returned to Iran in 2009 where he restarted his job as academic staff at the Shahrekord University of Medical Sciences. He is involved in the establishment of a "Health Sciences Research Center" at this University and in a multi-center project on the preparation of a national database for cardiovascular and cerebrovascular diseases.

List of Publications:

International Journals:

Masoodi R., Etemadifar S. and **Amiri M.** *Correlation between quality of life and perceived satisfaction in multiple sclerosis care givers. The effect of empowerment program* (Submitted).

Masoodi R., Etemadifar S. and **Amiri M.** *The effect of family-centered empowerment model on skill, attitude and knowledge of multiple sclerosis caregivers* (Submitted).

Masoodi R., Etemadifar S. and **Amiri M.** *The effect of family-centered empowerment model on quality of life of care givers with multiple sclerosis patients* (Submitted).

Amiri M, Janssen F. and Kunst AE. *The decline in stomach cancer mortality: exploration for the future in Europe* (Submitted).

Kunst AE, **Amiri M**, Bonsel GJ, and Janssen F. *The decline in stroke mortality. Exploration of future trends in seven Western European countries* (Submitted).

Amiri M, Janssen F. and Kunst AE. *The decline in ischemic heart disease mortality in seven European countries: exploration of future trends* (Submitted).

Aghadavoud Jolfaei M. and **Amiri M**. *Determinants of heart diseases: An overview* (In progress).

Amiri M, Takkenberg JJ, Boersma E. *Medication therapy in patients with stable coronary artery disease: An overview.* (In progress).

Boersma E, **Amiri M**, Takkenberg JJ. *Microsimulation modeling for clinical decision-making in individual patients with atherosclerotic disease: a concept* (In progress).

Kunst AE and **Amiri M**. *Longer generations, longer lives? Associations between body height and mortality trends among birth cohorts born between 1860 and 1940 in France and the Netherlands* (In progress).

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *Trends in stomach cancer mortality in relation to living conditions in childhood. A study of trends among birth cohorts born between 1860 and 1939 in seven European countries.* **Eur J Cancer.** 2006 Dec; 42(18): 3212-3218.

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Baghbanian P, Sarraf Zadegan N, Sadeghi M, Rafiei M, Tavassoli A, **Amiri M**. *Incidence and morbidity of coronary artery disease in Urban population in Isfahan, Iran*. (In progress).

Shojaei H, Shooshtaripoor J, **Amiri M**. *Efficacy of simple handwashing in reduction of microbial hand contamination of Iranian food handlers*. **Food Research International.** 2006; 39:525-529.

Amiri M, Kunst AE, Janssen F, Mackenbach JP. *The relation of trends in IHD and stroke mortality with infant mortality rate. A time series study among cohorts born between 1860 and 1939 in seven European countries.* **European Journal of Heart Failure Supplements**. 2004; 3(1): 137.

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Roya Kelishadi, Nizal Sarraf Zadegan, **Masoud Amiri**. *Zinc and Copper Status in Children with High family risk of premature Cardiovascular Disease*. **Annals of Saudi Medicine**. 2002; 22(5-6):291-4.

M. Amiri, R. Vakili, A. Jalali, N. Sarraf-Zedegan. *The hypocholesterolemic effect of brewer's yeast*. **Heart Views**. 2002; 2(4).

N.Sarraf-Zadegan, **M. Amiri**, S. Maghsoudloo. *Helicobacter pylori relation to acute myocardial infarction in an Iranian sample.* **Coronary Health Care**. 2001; 5:202-7.

Roya Kelishadi, Mahin Hashempour, Nizal Sarraf Zadegan, **Masoud Amiri**. *Trend of Atherosclerosis risk factors in children of Isfahan*. **Asian Cardiovasc Thorac Ann**. 2001; 9:36-40.

R Kelishadi, M Hashemi, N Sarraf-Zadegan, and **M Amiri**. *The trend of coronary heart disease risk factors in children and adolescents in Isfahan, Iran (1993–1999)*. **Atherosclerosis**. 2000; 151(1): 257.

N.Sarraf-Zadegan, **M. Amiri**, S. Maghsoudloo. *The association between antibody titers to helicobacter pylori, chronic coronary heart disease and acute myocardial infarction.* **Atherosclerosis**. 2000; 151(1): 28.

National (Iranian) Journals:

Naderi Gh, Sarraf Zadegan N, Boshtam M, Asgari S, Afyooni A, Jalali A, Najafian J, **Amiri M**, et al. *New risk factors for cardiovascular disease in Isfahan urban community.* **Journal of Kerman University of Medical Sciences**. 2004; 11(1): 28-35.

Sajadi F, Mohammadifard N, **Amiri M**, et al. *The prevalence of type II diabetes and its association with cardiovascular risk factors in Isfahan city, Iran*. **J of Mashhad University of Medical Sciences.** 2003; 46(81): 68-71.

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Masoud Amiri. *Basic Fundamentals of Clinical Epidemiology*. **Shahrekord Medicine Quarterly Magazine**. 1994 Sep.- Dec.; 5: 1-5.

Masoud Amiri. *Malaria and drug Resistance*. **Iranian Quarterly World Health Magazine**. March-June 1987; vol. 3; No. 1: 48-51.

PhD Portfolio Summary

Name of PhD student: Masoud Amiri
Erasmus MC Department: Public Health
PhD period: 2007 - 2010
Promotor: Prof. dr. G.J. Bonsel
Supervisor: Dr. A.E. Kunst

1. PhD training	Year	Workload Days(ECTs)
General academic skills		
- English Language	2002	4 (1.4)
- Introduction to Medical Writing	2003	4 (1.1)
- Working with SPSS for Windows	2003	1 (0.15)
- Integrity in Research	2006	3
- Writing Successful Grant Proposals	2010	1
In-depth courses		
- Master of Epidemiology, Netherlands Institute for Health Sciences (NIHES), Erasmus MC, Rotterdam, Netherlands		
o Erasmus Summer Program		
▪ Clinical Decision Analysis	2003	2.5 (0.7)
▪ Cohort Studies	2003	2.5 (0.7)
▪ Analysis of repeated measurements	2003	2.5 (0.7)
▪ Principles of Research in Medicine and Epidemiology	2003	5 (0.7)
o Core Curriculum		
▪ Study Design	2003	8 (4.3)
▪ Classical Methods for data-analysis	2003	12 (5.7)
▪ Public Health Research Methods	2003	8 (4.3)
▪ Qualitative Research and Survey Methods	2003	4 (1.4)
▪ Methodological Topics in Epidemiologic Research	2003	4 (1.4)
▪ Modern Statistical Methods	2003	8 (4.3)

- Advanced short courses
  - Analysis of time-varying exposures 2003 2 (0.6)
  - Environmental Epidemiology and Occupational Epidemiology 2003 3 (0.9)
  - Medical Demography 2003 5 (1.4)
  - Planning and Evaluation of Screening 2003 5 (1.4)
  - Decision Making in Health Care 2003 5 (1.4)
  - Cardiovascular Diseases Epidemiology (Cambridge University, UK) 2003 3 (0.9)

- Doctor of Science (D.Sc.) in Epidemiology, NIHES, Erasmus MC, Rotterdam, The Netherlands
  - Erasmus Summer Program
    - Bayesian Analysis 2004 2.5 (0.7)
    - Conceptual Foundation of Epidemiologic Study Design 2004 5 (1.4)
  - Advanced short courses
    - Design, Conduct and Analysis of Multicenter Studies 2004 2 (0.6)
    - Psychiatric Epidemiology 2004 2 (0.6)
    - Principles of Epidemiologic Data Analysis (Lunteren, Netherlands, By K. Rothman) 2004 5 (1.4)
    - Operational Research Applied to Health Sciences 2004 3 (0.9)
    - Internet Techniques for Health Care 2004 4 (1.1)

- COEUR courses, Dep. of Cardiology, Erasmus MC, Rotterdam, The Netherlands
  - Pathophysiology of Ischemic Heart Diseases 2005 5 (1.5)
  - Cardiovascular Pharmacology 2005 5 (1.5)
  - Cardiovascular Medicine 2005 5 (1.5)
  - Cardiovascular Clinical Epidemiology 2006 5 (1.5)
  - Cardiovascular Imaging and Diagnostics 2006 5 (1.5)
  - Atherosclerosis Research 2006 5 (1.5)

Seminars (Attending and Presenting)

- Bi-weekly seminars of Social Epidemiology Group	2003-2005	50
- Weekly seminars of Department of Public Health	2003-2005	80
- Weekly seminars of Department of Cardiology	2005-2006	30
- Cardiology and Vascular Medicine: Updates	2005	3 (1.5)
- Cardiology and Vascular Medicine: Updates	2006	3 (1.5)
- Weekly seminars of Department of Public Health	2009-2010	15

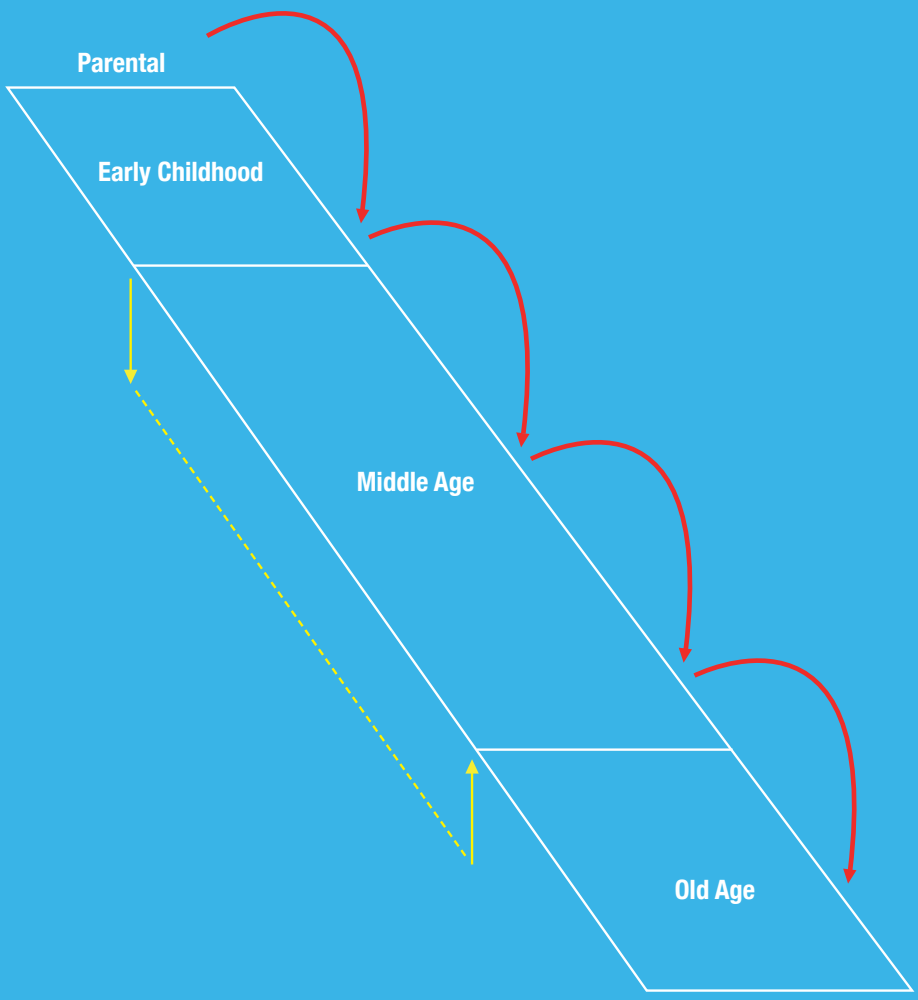
Presentation at International conferences

- 12th Annual Public Health Forum, Brighton, UK	2004	4 (1.4)
- Heart Failure Update 2004, Wroclaw, Poland	2004	4 (1.4)
- The 5th International Heart Health Conference, Milan, Italy	2004	4 (1.4)
- SER's 2004 meeting, Salt Lake City, USA	2004	4 (1.4)
- Third conference on Epidemiological Longitudinal Studies in Europe, CELSE3, Bristol, UK	2004	4 (1.4)
- The 7th World Congress on Gastrointestinal Cancer, Barcelona, Spain	2005	4 (1.4)
- 1st International Cancer Control Congress, Vancouver, Canada	2005	4 (1.4)

2. Other activities

		No. of Reviews
- Editorial Board of:		
o Stroke	2010-2011	
o Stroke	2009-2010	
o Preventive Medicine	Since 2009	
- Reviewer of :		
o Stroke	Since 2005	55
o Journal of Epidemiology and Community Health (JECH)	Since 2005	8
o American Journal of Epidemiology (AJE)	Since 2005	5

o McMaster Online Rating of Evidence	Since 2007	77
o European Journal of Clinical Investigation (EJCI)	Since 2008	3
o Libertas Academica	Since 2008	1
o Environmental Health Insights	Since 2008	1
o Journal of Internal Medicine (JIM)	Since 2008	1
o Journal of Isfahan Medical School (JIMS)	Since 2008	20
o European Journal of Cancer (EJC)	Since 2009	2
o Population Health Metrics Journal	Since 2009	1
o Journal of Shahrekord Medical University	Since 2009	2
o International Journal of Preventive Medicine (IJPM)	Since 2010	1
o Journal of Developmental Origins of Health and Disease	Since 2010	1


Parental
Early Childhood
Middle Age
Old Age