COMPRESSION AND PLASTICITY OF OLD-AGE MORTALITY

Frouke M. Engelaer

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"You have your way.
I have my way.
As for the right way,
the correct way,
and the only way,
it does not exist."

(Nietzsche, 1844-1900)

CONTENTS

Chapter 1

GENERAL INTRODUCTION

INTRODUCTION

This thesis entails research on the compression and plasticity of old-age mortality during the epidemiologic transition. The first chapters study the start of the epidemiologic transition in rural Ghana and describe the changes in mortality. This is followed by chapters on the compression of mortality and morbidity during the transition in Japan and the Netherlands. Finally, the last chapters concern the plasticity of mortality at old age. Studying old-age mortality during the epidemiologic transition is of great importance now that an increasing number of people reach old-age.

Life expectancy has increased all over the world from an average life expectancy of approximately 40 years before the epidemiologic transition to an average life expectancy that exceeds 80 years in post transitional countries today.[1] This major success in improving life expectancy was accompanied by a shift from child to old-age mortality and from infectious to non-infectious diseases.[2] The process of these mortality changes are described in the epidemiologic and demographic transition theories.

In 1971, it was Omran who first extensively described the different stages of the epidemiologic transition. He defined three classical stages, the first with high and fluctuating mortality, with an average life expectancy at birth varying between 20 and 40 years. This was followed by the second stage, when mortality declined at first gradually and then accelerated as soon as epidemic peaks became less frequent. This induced an increase in life expectancy at birth of 30 to 50 years on average. During the last stage mortality declined further, resulting in an average life expectancy that first exceeded 50 years. The first two stages were dominated by infectious diseases, whereas in the last stage the major cause of death was due to chronic diseases. The epidemiologic transition has been described as a sequential process of mortality changes.[2]

Now that mortality rates at old age are continuously on the decline, it is questioned whether the extra years are lived in good or in ill health.[3,4] How patterns of health and disease have evolved in the past and will evolve in the future is studied extensively. Part of this debate is centred around the compression of mortality and morbidity at old age.

The compression of mortality at old age indicates the distribution of the age at death in a population.[5] A population with no mortality compression at all would have completely age independent mortality risks. By contrast, maximum mortality compression would imply that a whole population would die simultaneously at the same age. Over the last

decades, there has been compression of old-age mortality, however, it is debated if the compression of mortality will reach a limit.[6,7] There is even more debate about the compression of morbidity, which precedes mortality. Some argue that our longer lives bring worsening health with an expansion of morbidity.[6,10,11] On the contrary, others believe that morbidity has also been compressed, even at old age.[9,10]

Finally, it is disputed whether mortality at old age is biologically fixed. The role of early life environment on old-age mortality is well documented. Infectious diseases and poor nutrition early in life have been linked with mortality in old age.[11-13] By contrast, there is controversy about the role of direct or late life effects on old-age mortality. Old-age mortality is often still thought to be fixed and it is generally believed that no significant reduction in mortality can be expected from environmental improvements later in life.[14] Some studies however, did show a direct health benefit and mortality reduction when introducing interventions at old age.[15-17] The debate of the plasticity of old-age mortality is of prime importance for the growing population of elderly and public health.

Aim of this thesis

To study the compression and the plasticity of old-age mortality during the epidemiologic transition.

Outline of this thesis

Chapter one provides a general introduction to the research in this thesis and describes the three main topics of this thesis: the epidemiologic transition, the compression of mortality and the plasticity of old-age mortality. The next two chapters are related to the epidemiologic transition. In **chapter two** we study the role of socioeconomic status and drinking water source on mortality and fertility decline at the start of the epidemiologic transition in rural Ghana. In addition we studied cause-specific mortality trends by making use of Verbal Autopsies. **Chapter three** covers a study on seasonal variation in mortality and cause-specific mortality in rural Ghana during the epidemiologic transition. We examine variation in mortality depending on the season and on the month of death. In the following **chapter four** we study the compression of mortality at old age during the epidemiologic transition in Japan and the Netherlands. Next to the compression of mortality, we study the compression of morbidity in **chapter five**. We decompose the trends in old-age mortality into trends of different morbidity measures. We examine the sex differences in these different measures of healthy life expectancy and discuss the compression of morbidity during the epidemiologic transition in the Netherlands. Following on the previous chapter, we argue that the increase in life expectancy is

accompanied by improved health in **chapter six**. In the final chapters we study different determinants of the plasticity of mortality at old age. First, **in chapter seven**, we study the plasticity of old-age mortality, in an experiment of nature in Japan which experienced an accelerated epidemiologic transition. Next, we examine another example of the plasticity of old-age mortality in a study on the effect of high intensive physical exercise on mortality risk in late life. We challenge the view that more physical activity is always better when it comes to health benefits. In **chapter eight** we test this hypothesis in a cohort of former Olympic athletes from different disciplines with various levels of physical intensity. Furthermore in **chapter nine**, we study the life expectancy of various historical artists compared to the elite in the Low Countries. Finally, we summarize the implications of our main findings concerning the compression and plasticity of old-age mortality and morbidity in **chapter ten.**

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I

THE EPIDEMIOLOGIC TRANSITION IN RURAL AFRICA

Chapter 2

DETERMINANTS OF THE EPIDEMIOLOGIC TRANSITION IN RURAL AFRICA: THE ROLE OF SOCIOECONOMIC STATUS AND DRINKING WATER SOURCE

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ABSTRACT

Many African countries experience a protracted epidemiologic transition that is different from the classical transition in western societies. The factors driving this protracted transition are largely unknown. In Northeast Ghana, we had the opportunity to study an ongoing epidemiologic transition and disentangle the effects of socioeconomic status and drinking water source. For nine years, we followed a cohort of almost 30,000 individuals for mortality and fertility rates. In addition, we obtained the causes of death by verbal autopsy, according to the standards of the World Health Organization. We found that mortality rates decreased by –5.0% annually (p<0.001) and that the main cause of death shifted from infectious diseases to non-infectious diseases (p=0.014). General fertility rates decreased by –12.7% annually (p<0.001) and child-women ratios decreased by –11.9% annually (p<0.001). There was no difference in the declines in mortality and fertility depending on socioeconomic status or the use of (un)improved drinking water source. Hence, factors other than socioeconomic status and drinking water source must drive the observed declines in mortality and fertility during the protracted epidemiologic transition. Identifying the specific determinants of the ongoing epidemiologic transition is of importance, as these identify targets to further improve public health in rural African countries.

INTRODUCTION

Since the description by Omran in 1971, the course of the epidemiologic transition is well known.[1] According to his model, the epidemiologic transition is a process with a decline in mortality followed by a decline in fertility. The first stage is characterised by pre-transitional patterns of health and disease, with pestilence and famine leading to high and fluctuating mortality together with high fertility. The average life expectancy at birth is around 20 to 40 years. During the second stage, mortality gradually declines as epidemic outbreaks become less frequent. The average life expectancy increases to 30 to 50 years. During the last stage, fertility rates start to decline and mortality is further reduced. Degenerative and man-made diseases prevail and the average life expectancy exceeds 50 years.

It is debated how currently developing countries, including those in rural Africa, experience the epidemiologic transition.[2-5] Many developing countries have started to experience a decline in mortality, but also in fertility.[6,7] Contrary to the classical sequential stages described above, these countries suffer from the coexistence of infectious and degenerative diseases, which is denominated as polarisation.[3,5,8] It has therefore been proposed to adopt a protracted model for the epidemiologic transition in developing counties, in which the classical stages overlap.[1,2,5] In addition, factors that have played an essential role in the classical epidemiologic transition, such as improvements in hygiene, access to improved drinking water, and socioeconomic status,[1] have been shown to determine the survival probability in rural Africa.[9,10] However, it is unclear whether these factors drive the declines in mortality and fertility during the current protracted epidemiologic transition.[2,6,7]

We had the opportunity to study an ongoing epidemiologic transition in rural Africa. In one of the least developed areas of Ghana, we followed a cohort of almost 30,000 inhabitants for nine years and registered survival and fertility. In addition, we obtained the causes of death by verbal autopsy. We were able to disentangle the effects of socioeconomic status and drinking water source, which are independently distributed in the area, on the changes in mortality and fertility.

METHODS

Ethics statement

As the majority of the study participants were unable to read and write, informed consent

was obtained orally. A consent form was read out to the participants in their local language, explaining the purpose and procedure of the study. For the verbal autopsies, the consent form from the verbal autopsy protocol of the World Health Organization (WHO) was read out. Consent was registered in the form of a thumb print. The entire procedure, including the text of the consent form, was approved by the Ethical Review Committee of the Ghana Health Service, the Medical Ethical Committee of the Leiden University Medical Center in Leiden, the Netherlands, and by the local chiefs and elders in the research area.

Research area and study population

This study was conducted in the Garu-Tempane District in the Upper East Region of Ghana. A map of the research area is provided in Figure 1. The Upper East Region is one of the least developed regions of Ghana, contrasting sharply with the more urbanised

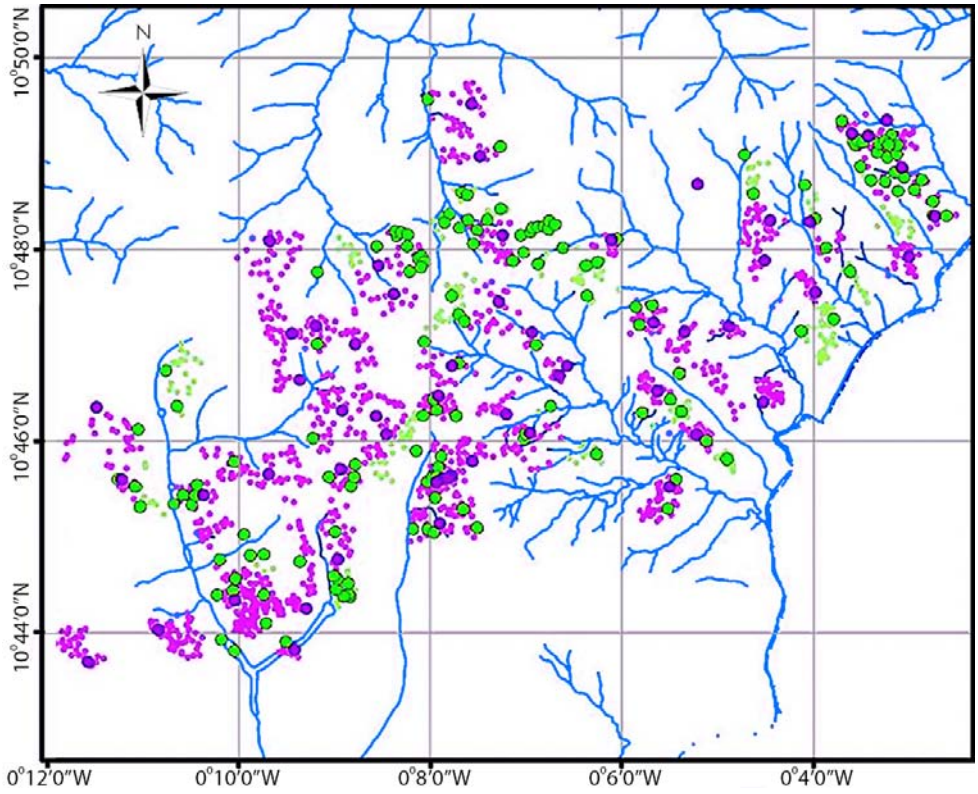

Figure 1. Map of the research area in the Garu-Tempane District in the Upper East Region in Ghana. Large purple circles denote improved drinking water sources, large green circles denote unimproved drinking water sources. Small circles denote households of which the colours indicate their primary drinking water source being improved or unimproved. Geographical and hydrological data were provided by CERGIS, University of Ghana in Legon, Accra, Ghana.

and affluent southern parts of the country.[11,12] The majority of the population are farmers, who execute the total agricultural process manually and without proper means of transportation, irrigation, and electricity.[9,13] The local economy is partly according to the Barter system, in which goods are directly exchanged for other goods or services.[11,12] Up to half of the population has not received any education.[11,12] Access to medical care is limited; most people rely on the aid of traditional healers.[11,12,14] Infectious diseases, such as malaria, meningitis, typhoid fever, and acute respiratory infections, are highly endemic and constitute the main causes of death.[14-17]

We kept a demographic registry of all inhabitants of a specified geographic area in the Garu-Tempane District measuring approximately 375 km^2 and comprising 32 villages. From 2002 through 2011 we visited the research area every year. Annual migration relative to the total study population was estimated to be 2% into and 1% out of the research area.[18]

Socioeconomic status

We measured the socioeconomic status of each household in 2007 based on the Demographic and Health Survey (DHS) method. In short, a DHS wealth index was calculated by listing the household property items of most value, such as cattle, bicycles, and iron roofing. The value of these items in US$ was estimated and summed for each household. For each individual, the socioeconomic status was classified as being below or above average according to the DHS wealth index of his household in 2007 split by the median. Detailed descriptions of this method have been published earlier.[9]

Water source

The main drinking water source was registered for each household in 2007. From around 1970 onwards, water boreholes were introduced throughout the research area by foreign non-governmental organisations (NGOs), independently of the socioeconomic status of surrounding households. Besides, a substantial part of the households depend on water from open wells and small rivers. Water from boreholes contains less pathogens and is, therefore, a safer source of water than water drawn from open wells and rivers, in which the pathogen content is higher.[10] In line with the classification of the WHO, we classified individuals living in 2007 in a household with access to a borehole as having access to an improved water source and those living in 2007 in a household with access to only open wells and rivers as having an unimproved water source.[19]

Mortality

For each year of follow-up we constructed life tables. The population size at the midpoint of each year of follow-up was estimated as the average of the two population sizes registered at the beginning and at the end of the year. Per year of follow-up, mortality rates were calculated as the registered number of deaths divided by the corresponding mid-year population. Since only live children were registered and the registry was updated with one-year intervals, mortality was missed for children born and deceased between two visits. Individuals below one year of age were therefore excluded from the analyses. Mortality rates were standardised to the population's distribution over age and sex in 2003.

Verbal autopsies

To obtain causes of death, we performed interviews in 2011 using validated verbal autopsy questionnaires from the WHO.[20-24] We translated the English questionnaires into the two major local languages, Bimoba and Kusaal. To test whether the questionnaires were translated correctly, we performed back-translations into English by independent translators. In cases of discrepancy, the final translation was decided upon after group discussions with native speakers and medical experts. In the research area, it is customary that one relative or caretaker from the same household closely cares for an ill or dying individual. The verbal autopsy interviews were principally performed with these relatives or caretakers of the deceased individuals. For deceased children, this concerned mostly the mother; for deceased elderly, this concerned generally one of the children living in the same household as the deceased individual.

From the total of 1,406 deaths, we were able to complete verbal autopsies for 1,263 (90%), of which 1,253 from the age of 1 onward. Verbal autopsy interviews could not be performed in 10% of the cases, mainly due to absence of an appropriate respondent at the time of the field visit. Following the guidelines of the WHO,[23,24] two physicians, blinded for each other's assessment, independently assigned causes of death to each verbal autopsy. If the assigned causes of death differed between the first two physicians, a third physician gave an independent assessment, not blinded for the assessment of the first two physicians. A cause of death was obtained if at least two of the physicians agreed; otherwise the cause of death was classified as unspecified. The causes of death were coded according to the International Classification of Diseases (ICD) VA-10 coding, as prescribed by the WHO verbal autopsy method.[23,24]

Fertility

We calculated two period measures of fertility for each year of follow-up. As the study population is polygamous with one man marrying up to four women, we calculated fertility measures for both females and males. The general fertility rate (GFR) was calculated by dividing the number of newborns by the number of females or males aged 19 to 44. The child-adult ratio (CAR) was calculated by dividing the number of children aged up to 5 by the number of females or males aged 19 to 49.

Statistical analyses

To explore determinants of the absolute mortality over the entire period of follow-up, we used Cox regression with left truncation of the longitudinal individual survival data. Changes in mortality rates over calendar years were determined and tested by Cox regression with calendar year as a covariate. Changes in the relative proportions of causes of death over calendar years were determined and tested by logistic regression with calendar year as a covariate. Changes in fertility rates over calendar years were determined and tested by Poisson regression with calendar year as a covariate and robust Huber-White sandwich estimation of variance. The analyses were also separately performed in three age groups representing children, adults, and elderly and after stratification by sex, socioeconomic status, and drinking water source. The analyses were performed in IBM SPSS Statistics 20 and Stata/SE 12.1.

RESULTS

Table 1 gives the characteristics of the study participants at baseline in 2002 and at the end of follow-up in 2011. During the full period of follow-up we registered 29,642 individuals from 1,719 different households with a median (interquartile range) individual follow-up of 8 (4–9) person-years. During this period we observed 4,069 newborns and 1,406 deaths.

Table 1. Characteristics of the study population

Year	2002	2011
Total number of individuals	17,178	24,048
Sex		
Male	8,191 (47.7%)	11,658 (48.5%)
Female	8,987 (52.3%)	12,390 (51.5%)
Tribe		
Bimoba	11,168 (65.0%)	15,991 (66.5%)
Kusasi	4,694 (27.3%)	6,438 (26.8%)
Other	1,316 (7.7%)	1,608 (6.7%)
Socioeconomic status		
Below average	5,762 (33.5%)	8,251 (34.3%)
Above average	11,088 (64.5%)	15,154 (63.0%)
Water source		
Unimproved	3,254 (18.9%)	4,530 (18.8%)
Improved	13,913 (81.0%)	19,020 (79.1%)

Data are given as numbers with percentages.

Figure 2 shows the age distributions of the study population at the start of the follow-up period in 2002 and at the end in 2011. A major shift can be seen in the constitution of the population, especially in the youngest age groups. In 2002, the group of 0-9 years made up 44.3% of the total male population and 37.6% of the total female population. In 2011 this had decreased to 27.1% and 25.9%, respectively.

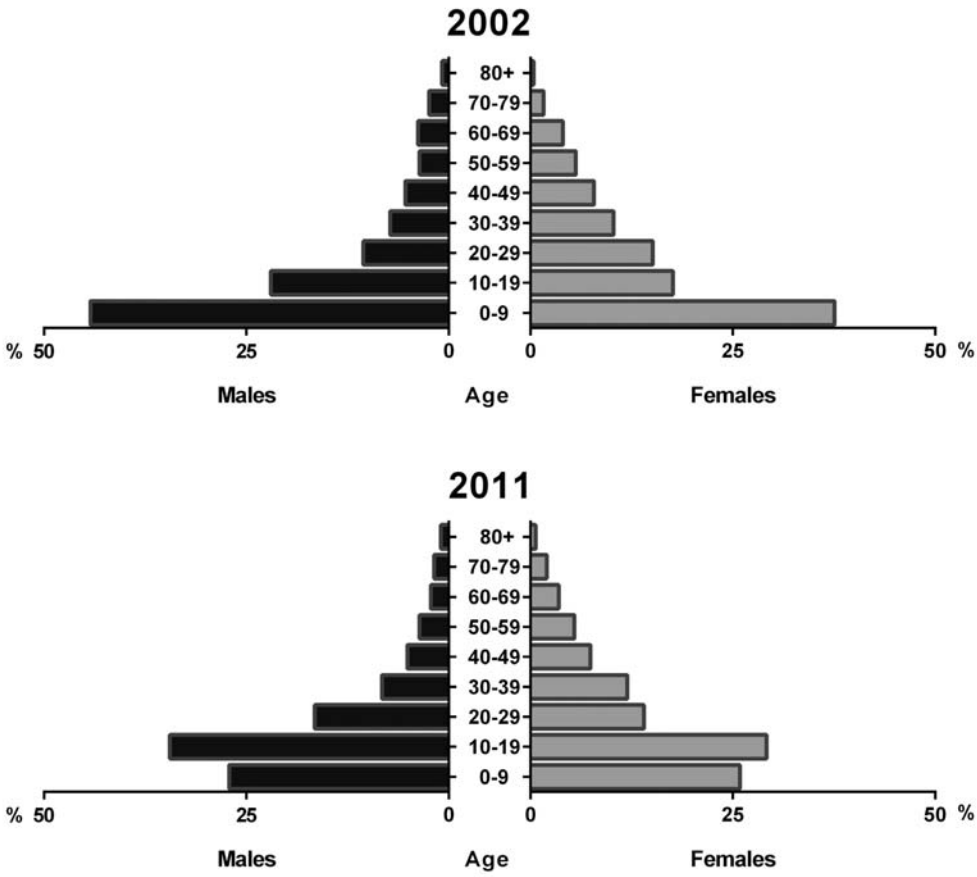

Figure 2. The sex-specific distributions over age groups of individuals in the study population in 2002 (upper pyramid) and 2011 (lower pyramid).

The absolute level of mortality over the entire follow-up period was dependent on age, sex, socioeconomic status, and water source. Mortality was higher in individuals of male sex (+41.3%, $p<0.001$), with a socioeconomic status below average (+30.7%, $p<0.001$), and for those drinking from an unimproved water source (+21.1%, $p=0.003$). The effects of sex, socioeconomic status, and water source on mortality were mutually independent and did not interact (all $p>0.05$). The effects of socioeconomic status and water source on mortality did not differ between the periods of follow-up before and after 2007 (Supplementary Table 1).

Supplementary Table 1. Socioeconomic status and water source as determinants of absolute mortality during 2002–2007 and during 2007–2011

	Difference in mortality (95%CI)		
	2002–2007	2007–2011	p value
Socioeconomic status			
Below average	+32.9% (+15.3; +103.8)	+24.8% (+5.7; +47.4)	0.696
Above average	Ref.	Ref.	
Water source			
Unimproved	+25.7% (+6.6; +48.4)	+15.6% (–5.3; +41.2)	0.579
Improved	Ref.	Ref.	

The difference in mortality between groups of socioeconomic status and water source have been calculated adjusted for sex as relative differences compared to the reference groups and are given with a 95% confidence interval (95%CI). The p values for interaction indicate that these effects do not differ between the periods 2002–2007 and 2007–2011. Ref.: reference group.

Table 2 shows the causes of death during the follow-up period from 2003 through 2011 as registered by verbal autopsy. Both the absolute number of deaths and the prevalences of infectious causes of death relative to those of non-infectious causes of death decreased during the period of follow-up.

Table 2. Causes of death during 2003–2011 as registered by verbal autopsy

Cause of death	2003–2005	2006–2008	2009–2011
Infectious and parasitic disorders	237 (51.5%)	195 (47.4%)	169 (44.2%)
Neoplasms	9 (2.0%)	10 (2.4%)	14 (3.7%)
Nutritional and endocrine disorders	3 (0.7%)	3 (0.7%)	0 (0.0%)
Disorders of the circulatory system	12 (2.6%)	9 (2.2%)	13 (3.4%)
Respiratory disorders	2 (0.4%)	3 (0.7%)	4 (1.0%)
Gastrointestinal disorders	20 (4.3%)	21 (5.1%)	20 (5.2%)
Renal disorders	1 (0.2%)	1 (0.2%)	0 (0.0%)
Mental and nervous system disorders	5 (1.1%)	3 (0.7%)	2 (0.5%)
Pregnancy- and childbirth-related disorders	3 (0.7%)	9 (2.2%)	7 (1.8%)
External causes	28 (6.1%)	36 (8.8%)	25 (6.5%)
Other specified causes	3 (0.7%)	0 (0.0%)	0 (0.0%)
Unspecified causes	137 (29.8%)	121 (29.4%)	128 (33.5%)
Total	460 (100%)	411 (100%)	382 (100%)

Data are given as numbers with percentages. Causes of death are categorised according to the International Classification of Diseases (ICD) VA-10 coding, as prescribed by the WHO.[22,23]

Figure 3A shows the decline in age-standardised mortality rates during the follow-up period from 2002 through 2011 for males and females. Mortality rates declined for males from 1,645 to 868 per 100,000 person-years and for females from 1,137 to 534 per 100,000 person-years. The overall mortality rate declined by –5.0% per calendar year (p<0.001). Mortality rates for infectious causes of death declined by –6.8% per calendar year (95%CI: –9.8 to –3.8, p<0.001) and mortality rates for non-infectious causes of death declined by –3.6 per calendar year (95%CI: –6.2 to –0.8, p=0.01). As shown in Figure 3B, during the follow-up period, the major cause of death shifted from infectious to non-infectious diseases (p=0.014).

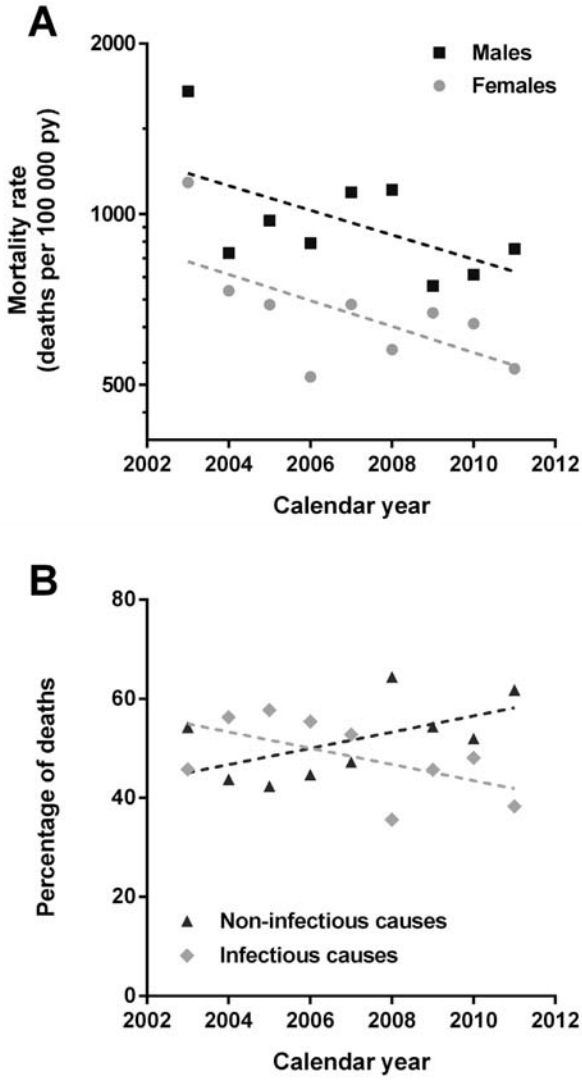

Figure 3.
A. Age-standardised sex-specific mortality rates per 100,000 person-years (py) over calendar years.
B. Relative prevalences of causes of death, classified as infectious or non-infectious, over calendar years as determined by verbal autopsy.

Table 3 shows the annual declines in mortality rate depending on age, sex, socioeconomic status, and water source. We studied the interaction between these determinants and the annual decline in mortality rate. There was no difference in the annual mortality decline between the age groups, sexes, groups of socioeconomic status, or types of water source (all $p>0.05$). Also, when studying the interaction between the various determinants and mortality in deaths due to infectious causes or non-infectious causes separately, no interaction was found.

Table 3. Determinants of the decline in mortality during 2002–2011

	Annual decline in mortality rate	95%CI	p value
Overall	–5.0%	(–7.0; –2.9)	< 0.001
Age group			
Ages 1–14 years	–4.2%	(–7.7; –0.5)	0.026
Ages 15–64 years	–6.6%	(–9.8; –3.3)	< 0.001
Ages 65+ years	–3.9%	(–7.4; –0.2)	0.038
Sex			
Male	–4.8%	(–7.5; –2.1)	0.001
Female	–5.2%	(–8.2; –2.1)	0.001
Socioeconomic status			
Below average	–5.3%	(–8.4; –2.1)	0.001
Above average	–3.6%	(–6.2; –0.8)	0.012
Water source			
Unimproved	–6.5%	(–10.7; –2.2)	0.004
Improved	–4.4%	(–6.7; –2.1)	< 0.001

The annual decline has been calculated as the relative change in the hazard ratio and is given with a 95% confidence interval (95%CI). Differences in the annual decline in mortality rate between age groups, groups of socioeconomic status, and groups of water source are non-significant.

Table 4 shows the annual declines in fertility rates. The general fertility rate (GFR) is the number of newborns per 1,000 females or males aged 19 to 44. The GFR decreased by –12.7% per year for females and by –11.9% per year for males. The child-adult ratio (CAR) is the number of children aged below 5 per 1,000 females or males aged 19 to 49. The CAR decreased by –15.0% per year for females and by –14.0% per year for males (all $p<0.001$). We observed no differences in these annual declines between groups of socioeconomic status or types of water source (all $p>0.05$).

Table 4. Determinants of the decline in fertility during 2002–2011

	General fertility rate			Child-adult ratio		
	Annual decline	95%CI	p value	Annual decline	95%CI	p value
Females						
Overall	–12.7%	(–16.9; –8.4)	< 0.001	–11.9%	(–12.5; –11.2)	< 0.001
Socioeconomic status						
Below average	–13.9%	(–20.0; –7.5)	< 0.001	–12.6%	(–13.4; –11.8)	< 0.001
Above average	–12.6%	(–15.7; –9.4)	< 0.001	–11.8%	(–12.4; –11.3)	< 0.001
Water source						
Unimproved	–11.0%	(–16.8; –4.8)	0.001	–12.0%	(–13.1; –11.1)	< 0.001
Improved	–13.6%	(–15.3; –9.7)	< 0.001	–12.1%	(–12.6; –11.5)	< 0.001
Males						
Overall	–15.0%	(–19.1; –10.8)	< 0.001	–14.0%	(–14.8; –13.2)	< 0.001
Socioeconomic status						
Below average	–15.6%	(–21.4; –9.4)	< 0.001	–14.4%	(–15.3; –13.4)	< 0.001
Above average	–15.3%	(–15.3; –12.1)	< 0.001	–14.3%	(–15.0; –13.7)	< 0.001
Water source						
Unimproved	–14.1%	(–19.4; –8.3)	< 0.001	–14.9%	(–15.9; –13.8)	< 0.001
Improved	–15.7%	(–19.4; –11.8)	< 0.001	–14.1%	(–14.7; –13.4)	< 0.001

The annual decline has been calculated as the relative change in the general fertility rate or the child-adult ratio and is given with a 95% confidence interval (95%CI). Differences in the annual decline in mortality rate between age groups, groups of socioeconomic status, and groups of water source are non-significant.

Figure 4 shows the annual decline in fertility rates during the follow-up period from 2002 through 2011 for males and females. Figure 4A displays the decrease in the GFR from 236 to 60 newborns per 1,000 males and from 186 to 56 newborns per 1,000 adult females. Figure 4B displays the decrease in the CAR from 1,459 to 454 children per 1,000 males and from 1,138 to 419 children per 1,000 females. During the follow-up period, the trends in fertility of males and females converged. When studying the interaction between sex and fertility decline, there was no interaction between sex and the decline in GFR (p=0.450). However, the interaction between sex and CAR was significant (p<0.001).

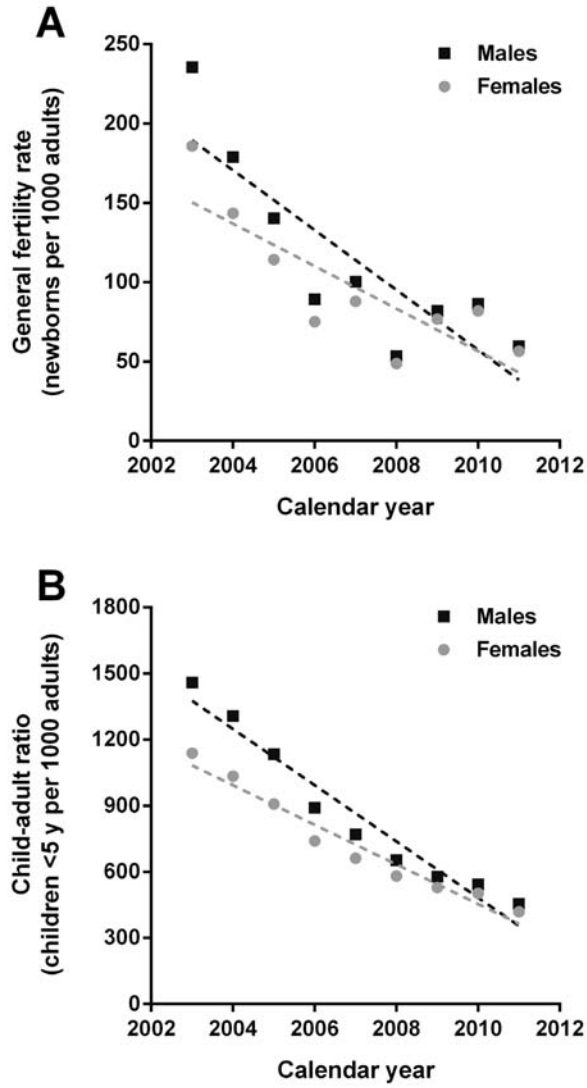

Figure 4.
A. General fertility rate as the number of newborns per 1,000 females or males aged 19 to 44 over calendar years.
B. Child-adult ratio as the number of children aged up to 5 years (y) per 1,000 females or males aged 19 to 49 over calendar years.

DISCUSSION

This study describes the epidemiologic transition in rural Africa during a follow-up period of nine years. We observed declines in both mortality and fertility. At the same time, the main cause of death changed from infectious diseases to non-infectious diseases. These transitions were not dependent on socioeconomic status or drinking water source.

Different models have been proposed to describe the declines in mortality and fertility during the various stages of the epidemiologic transition.[1,2] The validity of these theories highly depends on the time and place of a transition.[1,6,7] The transition in currently developing countries, as described by the protracted transition model, is expected to differ in two ways from the classical transition, as has been experienced by the current industrialised countries. Firstly, while a decline in mortality is classically regarded as a prerequisite and precursor of a decline in fertility, these stages are not sequential but overlap in developing countries. Secondly, the classical transition is mainly driven by socioeconomic rather than medical factors, since a high socioeconomic status improves standards of living, health habits, hygiene, and nutrition.[1] However, in developing countries, the role of socioeconomic status and hygiene remains unclear.

In line with the protracted transition model, we observed concurrent declines in mortality and fertility and a coexistence of infectious and non-infectious diseases, known as a double burden of disease.[3,5,8] During the follow-up period we did not observe the start of the transition in the research area and our conclusions are confined to the follow-up period. Therefore, we cannot make inferences on the start of the declines in mortality and fertility and their relative timing. Furthermore, we observed that the male and female fertility trends converged during the period of follow-up. This finding could point to a decrease in the prevalence of polygamy, which would be in line with an ongoing epidemiologic transition.

It is tempting to hypothesise about possible elements that have contributed to the epidemiologic transition in rural Ghana. Previously, we have described socioeconomic status and water source as determinants of absolute mortality over age in our study population. Risk of mortality is increased for those with a low socioeconomic status and those who drink from unimproved water sources.[9,10,25] Although socioeconomic status and water source determine survival, they did not relate to the declines of mortality and fertility during the epidemiologic transition. Possibly, these declines have started earlier in groups with a relatively high socioeconomic status or access to an improved water

source, so that the absolute levels of mortality differ, but the declines in mortality do not differ.

Importantly, socioeconomic status and water source have likely been stable factors in the research population. This assumption is supported by the fact that the effects of socioeconomic status and water source on mortality did not differ between different periods of follow-up. It has been shown that the heritability of socioeconomic status in pre-transitional societies is substantial, especially when material wealth is of relatively more importance than embodied or relational kinds of wealth, as is true for agricultural societies such as in this research area.[26-29] In our study population, socioeconomic status has been primarily determined by material household property that is passed from parents to children, such as cattle, vehicles, and iron roofing.[9,11,12] Migration has been related to rapid changes in socioeconomic status,[30] but annual migration in this research area was low. In general, if socioeconomic status has changed for all groups in the research area, relative differences remain stable. Concerning water sources, households predominantly draw from the most nearby and easily accessible source. As improved water sources, boreholes have been constructed in the research area by western non-governmental organisations from 1970 onward.[10,18] Since then, new boreholes have scarcely been introduced. During our nine years' presence in the research area, we only incidentally found a dysfunctional borehole. This is in line with our informal observation that the water infrastructure did not change significantly during this period. The use of boreholes as opposed to rivers and open wells is mainly dependent on their distances to the household. In line with this, we found no association between socioeconomic status and water source on the annual declines in mortality and fertility. In another district close to our research area, it has been documented that there is almost no relation between water source and socioeconomic status.[31]

It is possible that socioeconomic status does not contribute to the epidemiologic transition in this study population due to the local economic system, wherein goods are directly exchanged for other goods or services, according to the Barter system. For the transition to occur in such an economy, small-scale developments that raise the productivity of the agricultural sector and that facilitate the trade with other regions are more important, but are, at the same time, more difficult to record than material wealth.[32] Examples of such investments are the provision of land development techniques, means of transportation, and education. In our study population, these requisites have long remained deficient, but are slowly developing.[9] There is little incentive to produce more food than locally needed, since crops are low in value and cannot be easily exported outside the area.

It has been suggested that public health measures especially induce a transition in rural African countries.[1,4,6,7,33-36] This could be true for our study population, where public health services have improved during the follow-up period. In 2003, a national health insurance was established. Its national coverage rose from 18% in 2006 to 62% in 2009.[36] In our study population, its coverage rose from 4% in 2007 to 24% in 2011. People enrolled in this health insurance program are more prone to attend formal medical care.[34,36] Moreover, the coverage of immunisation has risen, thanks to vaccination programs for diphtheria, tetanus, pertussis, measles, hepatitis B, and polio. Furthermore, mass treatment of parasitic diseases has taken place in our research area.[15] Such public health measures have probably been of benefit for the population in general, regardless of socioeconomic status and water source.

The epidemiologic transition in rural areas has several important implications for society. The coexistence of both infectious and non-infectious diseases is a double burden to public health. We have argued earlier that the absence of a sedentary lifestyle prevents the occurrence of cardiovascular disease in our study population.[16] The progression of agricultural techniques and public health is likely to be accompanied by changes in lifestyle that strongly increase the risk of non-infectious diseases.[2,37] Currently, the primary focus in rural areas is on cure, thereby neglecting prevention and care.[2] Moreover, developing countries have limited resources to establish an effective response to the double burden of disease.[38] More knowledge on the epidemiologic transition, its underlying determinants, and the burden of disease can help rural African regions to develop more effective public health interventions.

A strength of this study was that follow-up was available for the entire population within the research area for a period of nine years. Consequently, the mortality and fertility measures that we have documented represent true outcomes for this population. A limitation of this study is that it lacks reliable information on the survival of children aged less than 1. To estimate mortality in this age group, we executed interviews in 2011 and registered whether children had been born and died between our field visits in 2010 and 2011. From this, we estimated the mortality rate to be 3,313 per 100,000 person-years. This number accords with the mortality rate of this age group as reported for the entire Upper East Region, being 3,300 per 100,000 births.[12] Although we cannot draw conclusions about possible changes in mortality in this age group, this limitation does not undermine our conclusions for the other age groups. A further limitation is that we performed all verbal autopsy interviews in 2011. Hence, the recall period varied from 0 to 9 years. However, the percentages of uncompleted verbal autopsies and of

unspecified causes of death were distributed equally over the years. Next, declines in mortality and fertility were only related to socioeconomic status and water source. These two parameters were known for the entire population, contrary to other parameters measured in selected subgroups,[10,16,17] and were strongly related to mortality.[9,10,25] Finally, we lack some information on women's fertility that would have been valuable to describe the epidemiologic transition, such as changes in age at first birth, time between births, parity, and cultural values related to fertility.

In conclusion, in rural Ghana, mortality and fertility decline in parallel during the epidemiologic transition. Socioeconomic status and water source do not play a role in these declines. Studying the epidemiologic transition in developing countries can direct to specific public health interventions that can improve public health in these countries.

Authors' contributions

FME, JJEK, DvB, UKE, and RGJW conceived the study and designed the study protocol; FME, JJEK, DvB, and UKE carried out the data collection; FME and JJEK carried out the analyses; all authors carried out the interpretation of the data; FME and JJEK drafted the manuscript; DvB, UKE, and RGJW critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. RGJW is guarantor of the paper.

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Chapter 3

SEASONAL VARIATION IN CHILD AND OLD-AGE MORTALITY IN RURAL GHANA

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ABSTRACT

Mortality in tropical countries varies considerably from season to season. As many of these countries have seen mortality moving from child mortality to old-age mortality, we have studied seasonal variation in child and old-age mortality in a rural area in Ghana that currently undergoes an epidemiologic transition. In an annual survey from 2002 through 2011, we followed 29,642 individuals and obtained the cause and month of death from 1,406 deceased individuals by making use of verbal autopsies. When comparing the seasons, we observed a trend for higher mortality during the wet season. When comparing separate months, we observed 34% more deaths than expected in September (95% CI:1.04-1.69, p=0.024) at the end of the wet season and 43% more deaths in April (95% CI:1.13-1.80, p=0.004) at the end of the dry season, while there were 42% less deaths than expected in December (95% CI:0.52-0.70, p=0.003) shortly after the wet season. Cause-specific analysis indicated that the peak at the end of the wet season was due to excess mortality from infectious diseases in children and older people alike, whereas the peak in old-age mortality at the end of the dry season was due to non-infectious causes in older people only. Taken together, our data suggest that during the epidemiologic transition, mortality not only shifts from child to old-age and from infectious to non-infectious, but also from the wet to the dry season.

INTRODUCTION

Worldwide, there is variation in mortality depending on the season.[1-7] In tropical countries with a distinct dry and wet season, this is characterised mostly by excess mortality during the wet season.[8,9] Most studies analysing seasonal mortality have examined these patterns only for mother and child mortality.[10,11] It was found that excess mortality in the wet season is best explained by an increase in gastrointestinal infections and malaria.[8-11]

Currently, many of these tropical countries are experiencing an epidemiologic transition, with mortality moving from child mortality to old-age mortality.[12-15] This is primarily due to improved living conditions and a lower risk to die from infectious diseases.[15-17] At the same time deaths from chronic diseases are on the rise.[14] It is yet unclear how the seasonal variation in mortality has evolved now that many of these countries have undergone major changes in their mortality patterns.

In this study, we have analysed seasonal patterns of mortality among children and older people from a unique population in rural Ghana, which currently experiences the epidemiologic transition. Additionally, we collected the causes of death using verbal autopsies. We first studied whether the dry and the wet season involved a proportional number of deaths and second, whether each month comprised an equal number of deaths. We stratified for age and studied the causes of death to further explore the observed patterns.

MATERIALS & METHODS

Study area & population

The study is conducted in the Garu-Tempane district, which is situated in the Upper East region of Ghana. This region is far less developed than the southern part of Ghana and is highly endemic for malaria (85% of the population is infected with *Plasmodium falciparum*), typhoid fever, meningococcal disease and intestinal helminth infections.[18-22] The research area is situated close to the village of Garu and measures approximately 375 km^2, with almost 30,000 individuals living in around 40 villages. The people in the research area live in polygamous extended families, with an average of 15 people per household. The families live together in compounds: clay structures with thatched roofs, connected by clay walls.[23,24] There are 1,719 compounds in the research area. Most people rely on traditional healers, which are equally distributed throughout the area. Although there are a few basic health care facilities (Community-based Health Planning and Services compounds) in the area, there is no medical doctor present, and the nearest hospital is 40 km away.[21] The vast majority of the population are farmers, and the total agricultural process is done by hand. The local economy is dominated by the Barter system, where goods are directly exchanged for other goods or services.[25,26] From around 1970 onwards, water boreholes that use hand operated pumps to deliver ground water, were introduced to the region. These boreholes were distributed throughout the area by a non governmental organisation, independent of the socioeconomic status of surrounding households. Drinking water source has been assessed at the household level in 2007. In spite of the boreholes, some of the villages still depend on rainwater and water from small streams that flow through the area. Water from boreholes has been found to contain less pathogens and is considered to be safe drinking water, water drawn from either open wells or from rivers was found to contain more pathogens and is therefore considered to be unsafe drinking water.[22]

Climate

The research area is characterized by a pronounced dry and wet season. The area is drier than southern areas of Ghana and is proximate to the Sahel and the Sahara. The dry season is influenced by the Harmattan, a dry and dusty desert wind that blows from the northeast. During this period the humidity is very low and rainfall is entirely absent, resulting in hot days and cool nights. The wet season is influenced by the tropical maritime air mass, which provides the area with rain.[27,28] Exact data of temperature and rainfall in the research area were available from a research project between 1991 and 2004.[23] (Ghana Government Data from the Garu Tempane district provided by Roger Blench)

Between 1991 and 2004, the daily mean temperature is 28.5 ˚C. The mean minimum monthly temperature is 25 ˚C, whereas the mean maximum monthly temperature is 32 ˚C. From November to March, the minimal night temperature is 15 ˚C and the maximum day temperature 45 ˚C. The annual mean temperature was 28.9 ˚C and the annual amount of precipitation 996 mm.

Verbal autopsies

To obtain the causes and time of death, we used the validated verbal autopsy questionnaires from the World Health Organization (WHO).[29-31] In 2011 we performed the verbal autopsies in the area to identify the causes of death in both elderly and children. The WHO verbal autopsy method is based on a semi-structured questionnaire to conduct interviews with relatives or caretakers of deceased individuals. We have translated the English questionnaires into the two major local languages; Bimoba and Kusaal. To test whether the questionnaires were translated correctly, we performed back translations by an independent translator. In cases of discrepancy, the final translation was decided upon after group discussions with native speakers and medical experts. We trained local people from the two main tribes in the area to perform the interviews in people from their tribe in the field. They were instructed to search for the most appropriate respondent, which was in most cases a relative or caretaker of the deceased. The questionnaires were systematically checked by supervisors from the field staff who regularly participated during the field visits as well. From the total of 1,406 individuals that had died from 2003 to 2011 and were registered in the database, we were able to complete 1,263 verbal autopsies (90%). From 10% we were not able to perform a verbal autopsy interview due to various reasons, such as absence at the time of the field visit, no appropriate respondent found or in a few cases refusal to participate. Informed consent was obtained by reading the consent statement from the verbal autopsy protocol of the World Health Organisation aloud in the local language.[29] Consent was documented by signature or thumbprint of the participant. The study was approved by the Ghana Health Service Ethical Review Committee. To assign the causes of death we used a physician review method. In the first round, two physicians assigned the causes of death independently, blinded for each other. The agreement of the first two physicians in assigning the causes of death was in line with other studies using verbal autopsies with an average kappa of 0.41. If there was discrepancy between the first two diagnoses of the physicians, a third physician, who was not blinded for the diagnoses of the first two physicians, gave an independent assessment. A cause of death was determined if at least two of the medical doctors agreed, otherwise the cause of death was classified as unknown. To code the causes of death we used the International Classification of Diseases (ICD) VA-10 coding,

according to the WHO verbal autopsy method.[31] To study the seasonal variation in mortality we compiled the various causes of death into two categories: infectious diseases and non-infectious diseases. To test the repeatability of the verbal autopsy interviews, we performed re-interviews in a random selection of 10% of the original interviews. We tested the agreement between the diagnosis of the original interview and the re-interview and found an agreement with a kappa of 0.41. Since a proportion of the local population is not used to using dates and months, data on the exact month of death was not always available. Therefore, we additionally added a question about the season of death (dry or wet).

Socioeconomic status

In 2007 we measured socioeconomic status at the household level using the Demographic and Health Survey (DHS) methods, specifically designed for our research area.[32] First we developed a questionnaire to assess the socioeconomic status of the study participants by using a listing technique whereby we asked people from different villages of the research area, in focus group discussions, to list the household items of most value. We than applied the method used to calculate the DHS-wealth index. For analysis, the results of this DHS-wealth index were split by the median in households with low socioeconomic status (poor) and households with high socioeconomic status (rich). For a detailed description of these methods we refer to an earlier publication of this study.[33]

Statistical Analysis

We used a Fishers exact test to assess whether the observed monthly mortality was significantly different than expected under the null-hypothesis that seasonal variation is absent.[34] We calculated the confidence intervals of the count data based on a Poisson distribution.[35,36] To test for agreement between physicians who assigned the causes of death, and the repeatability of the verbal autopsy interview, kappa values were calculated. All these analyses were carried out using SPSS 18 (SPSS Inc., Chicago, IL, USA). Additionally, we further analysed the data using STL: a seasonal-trend decomposition procedure based on Loess.[37] This is a filtering procedure for decomposing a time series into trend, seasonal and remainder components and was carried out in R.

RESULTS

From 2002 through 2011 we followed 29,642 individuals for mortality in the Garu Tempane District of the Upper East Region of Ghana, as shown in Figure 1.

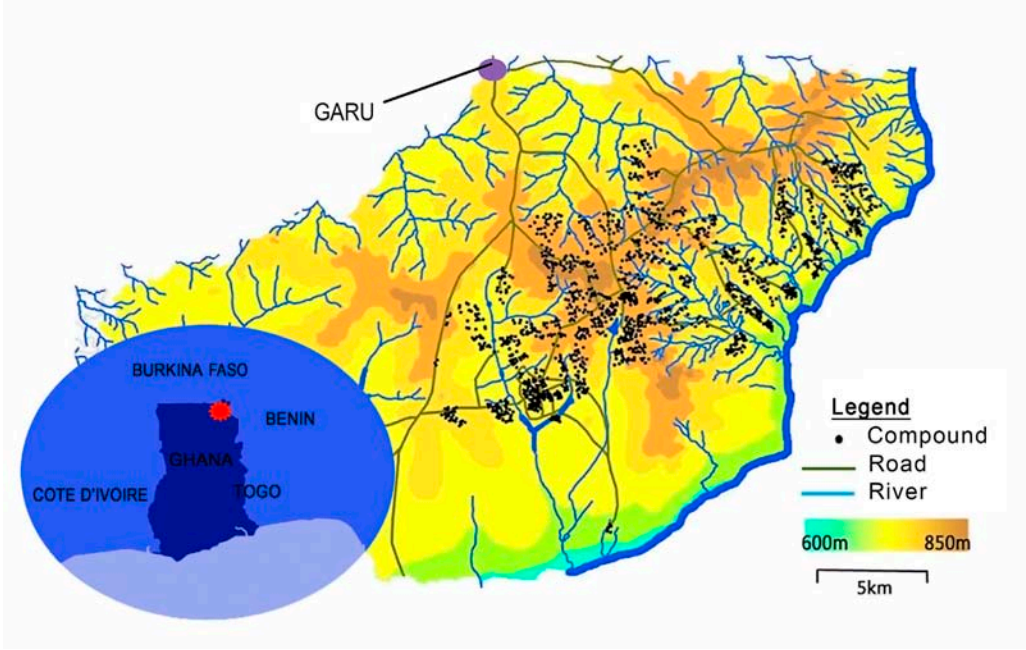

Figure 1. Map of the research area in the Garu-Tempane District in the Upper East Region in Ghana.

The general characteristics of the study population are summarized in table 1. Most individuals lived in compounds with a high socioeconomic status (61%) and had access to safe drinking water (79%). The Bimoba tribe was most represented (66%), followed by Kusasi (26%). Other tribes, including Mamprusi and Fulani together made up to 8% of the deceased individuals.

Table 1. Characteristics of the study population from 2002 trough 2011.

	Study population n (%)	Number of deaths n (%)
Total	29,642 (100%)	1,406 (100%)
Sex		
Men	13,628 (46%)	786 (56%)
Women	16,014 (54%)	620 (44%)
Socioeconomic status		
Poor	10,205 (35%)	580 (41%)
Rich	18,414 (61%)	795 (57%)
Unknown	1,025 (4%)	31 (2%)
Drinking water		
Unsafe	5,677 (19%)	308 (22%)
Safe	23,428 (79%)	1,095 (78%)
Unknown	537 (2%)	3 (0%)
Age		
Children (0-14)	12,613 (43%)	401 (29%)
Adults (15-64)	15,369 (52%)	494 (35%)
Elderly (65+)	1,660 (6%)	511 (36%)
Tribe		
Bimoba	19,451 (66%)	893 (64%)
Kusasi	7,777 (26%)	418 (30%)
Other/Unknown	2,415 (8%)	95 (7%)

During the period of follow-up we observed 1,406 deaths, of which 786 (56%) were men and 620 (44%) were women. Indicative for the on-going epidemiologic transition we observed a decline in the ratio of infectious- over non-infectious causes from 1.2 to 0.7 over the nine years observation period (p for trend 0.014). From the total of 1,406 deceased individuals, we were able to obtain the season of death for 1,061 (75%) individuals and for 627 (45%) we could additionally recollect the exact month of death. These three groups did not differ significantly in their baseline characteristics or recall period.

The monthly variation in the average temperature and rainfall in the research area is presented in Figure 2. Temperature ranges from a mean of 26.8 ˚C in August to 32.4 ˚C in March and April, whereas rainfall varies from a mean of 0.2 mm in January and December to a peak of 263.1 mm in August. The area has two distinct seasons, a dry

season that lasts for seven months from October to April and a wet season that lasts for five months from May to September.

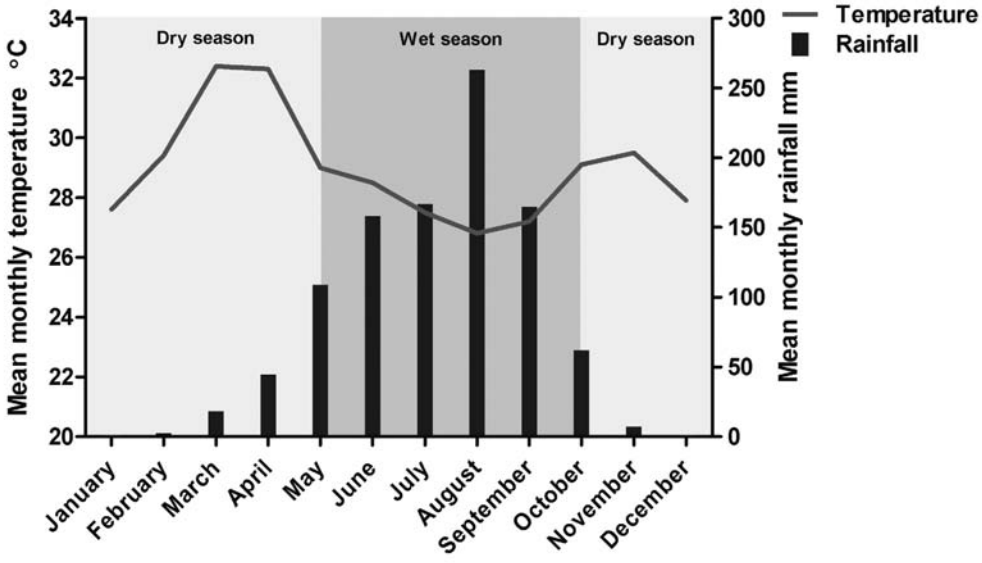

Figure 2: Climatologic variation in the research area, indicated by the mean monthly temperature and mean monthly rainfall. The annual mean temperature was 28.9 ˚C and the annual amount of precipitation 996 mm. Source: Ghana Government, provided by Roger Blench.

We first analysed the observed number of deaths per month between the wet and the dry season (table 2). Overall there was a trend for higher mortality during the wet season. When stratifying for socioeconomic status, we observed higher mortality during the wet season in both rich and poor households. Finally, we observed that only people who made use of safe drinking water had lower mortality during the wet season.

Table 2. Number of deaths per month in wet and dry season for various subgroups.

	Wet season		Dry season	
	Number of deaths per month	(95% CI)	Number of deaths per month	(95% CI)
All deaths	95	(77-116)	84	(67-101)
Age				
Child (0-14 years)	26	(17-38)	21	(14-33)
Adult (15-64 years)	33	(23-46)	30	(20-43)
Old-age (65+ years)	36	(25-50)	32	(22-45)
Socioeconomic status				
Poor	38	(27-52)	33	(23-46)
Rich	56	(42-73)	49	(36-65)
Drinking water				
Unsafe	26	(17-38)	18	(11-29)
Safe	59	(45-76)	66	(51-84)

* The number of deaths per month were calculated by dividing the observed number of deaths in a season by the number of months in that season. CI = confidence interval.

Next, we examined the longitudinal data series in a seasonal-trend decomposition procedure. We decomposed the mortality data in a seasonal component, a secular trend and remaining variation, as shown in Figure 3. The model identified mortality peaks in April and September and low mortality in December. When comparing the separate months, we observed 34% more deaths than expected in September (95% CI: 1.04-1.69, p=0.024) at the end of the wet season and 43% more deaths in April (95% CI: 1.13-1.80, p=0.004) at the end of the dry season, while there were 42% less deaths than expected in December (95% CI: 0.52-0.70, p=0.003) shortly after the wet season. This seasonal variation overlapped for 44% with the data, while the secular mortality trend overlapped with 51% of the data. Comparing the seasonal trends over calendar time, the mortality peak in April was most pronounced in recent years (data not shown).

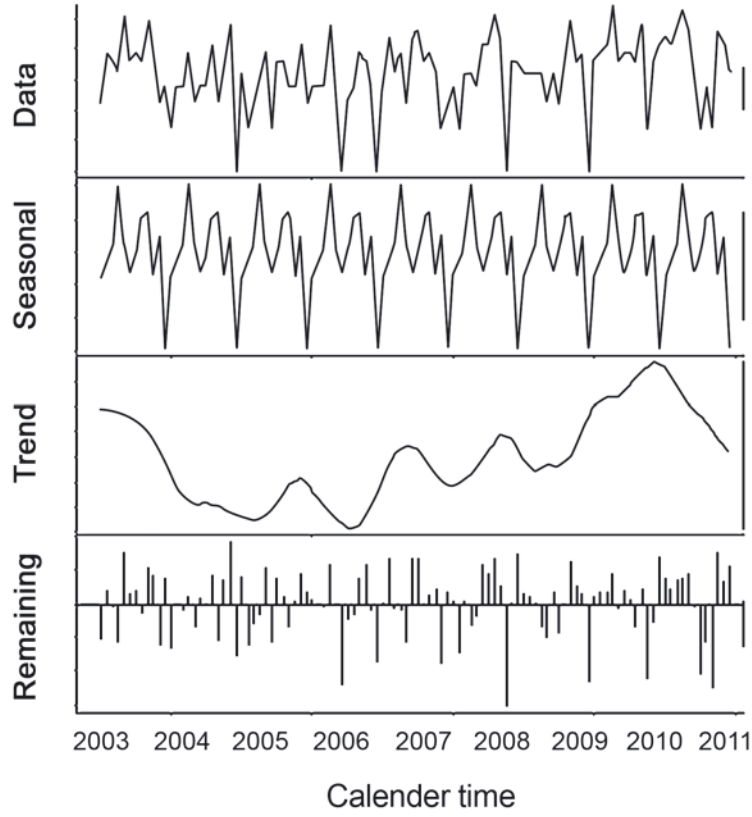

Figure 3. The seasonal variation in mortality over the months from 2003 through 2011. This filtering procedure decomposes the raw data into a seasonal component, a trend and remaining variation.

To further explore the causes of the seasonal variation, we stratified for child and old-age mortality. Figure 4 illustrates that child mortality shows one mortality peak during the wet season in September with 74% (95% CI: 1.09-2.63, p=0.021) more deaths than expected, whereas there was 69% less lower than expected in January (95% CI: 0.08-0.78, p=0.007). In contrast, old-age mortality shows two mortality peaks: in September there were 54% (95% CI: 1.06-2.18, p=0.025) more deaths than expected and in April there were 40% (95% CI: 1.06-2.18, p=0.098) more deaths than expected. In December there were 39% less deaths than expected (95% CI: 0.32-1.04, p=0.073).

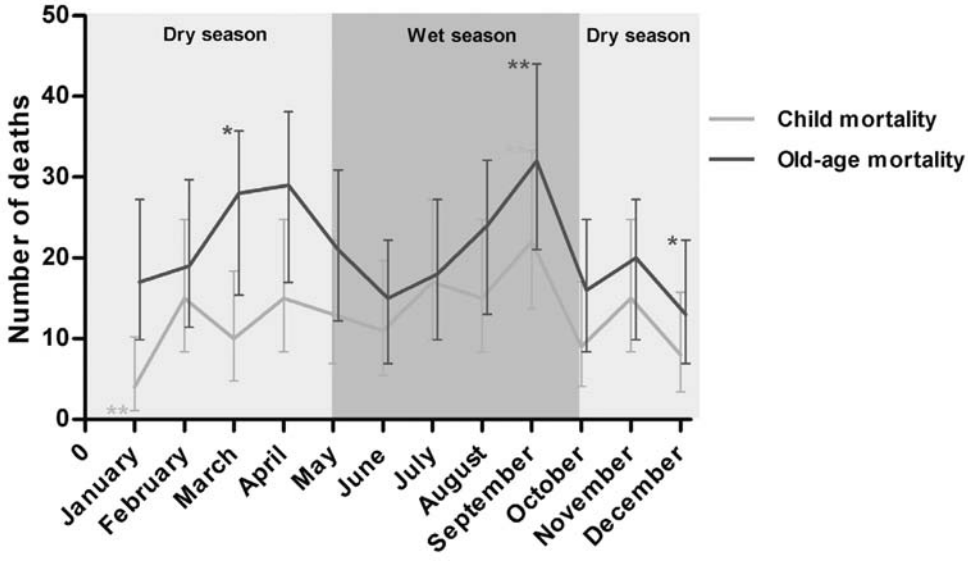

Figure 4. Seasonal variation in child mortality and old-age mortality. Mortality is expressed as number of deaths per month with error bars indicating 95% confidence interval. Stars indicate whether the observed number of deaths in that month are significantly higher than expected. *p<0.1, ** p<0.05

Figure 5 shows the seasonal variation in the number of deaths due to infectious- and non-infectious causes. Among children (panel A), 68% of the deaths were due to infectious diseases and appeared 75% (95% CI: 1.42-2.19, p=0.057) higher in September at the end of the wet season. In January there was 66 % (95% CI: 0.19-0.59, p=0.048) mortality from infectious diseases. Mortality from non-infectious causes appeared to be equally distributed over the months. Among older people (panel B), infectious and non-infectious causes of death were equally common. Mortality from infectious causes in old age peaked in September with 74 % (95% CI: 0.97-2.87, p=0.061) higher mortality, whereas mortality from non-infectious causes peaked with 52% higher mortality in both September and April, (95% CI: 0.87-2.47, p=0.0138).

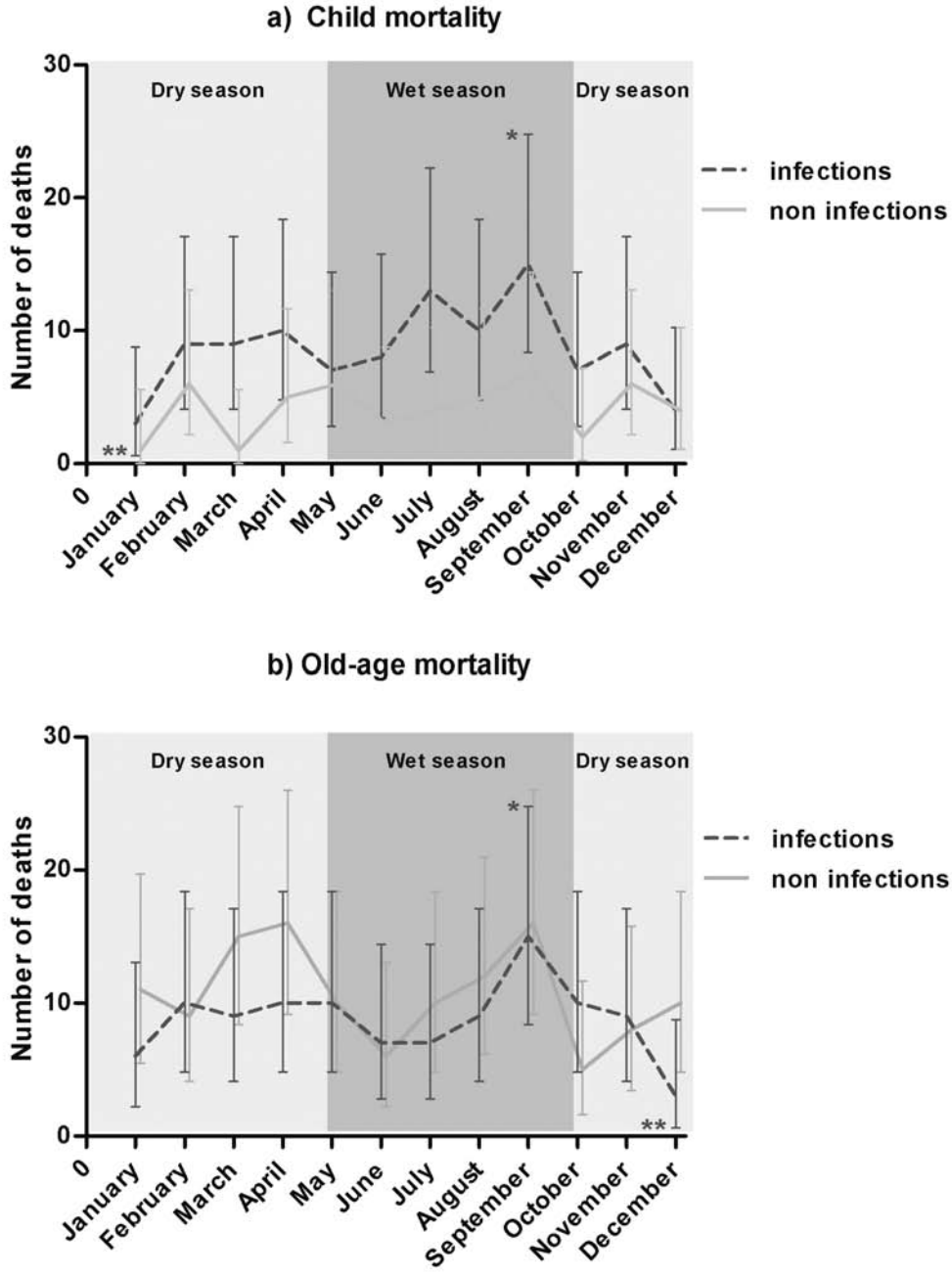

Figure 5. Seasonal variation in mortality from infectious and other causes in child mortality (panel A) and old-age mortality (panel B). Mortality is expressed as number of deaths per month with error bars indicating 95% confidence interval. Stars indicate whether the observed number of deaths in that month are significantly higher than expected. *p<0.1, ** p<0.05

DISCUSSION

In a rural area in Ghana, we have observed a mortality peak in the wet season for both child and old-age mortality that can be explained by an increased number of deaths from infections. There was however, a second mortality peak at the end of the dry season among older people due to non-infectious causes. There was low mortality in the months succeeding the wet season.

Variation in mortality is both, driven by geographical factors such as climatic influences and by individual or household determinants.[38] Therefore, we additionally studied the role of socioeconomic status and the use of (un)safe drinking water. Mortality during the wet season was higher for people from both rich and poor households. Although the effect size was similar for both groups, it was only significant in the (larger) group of the rich. By contrast, water source did influence the seasonal variation in mortality as indicated by the higher mortality during the wet season in individuals using unsafe drinking water. It is tempting to speculate that the observed excess mortality during the wet season in people drinking unsafe water could be explained by contamination of drinking water during the wet season, when unsafe open wells are flooded with surface water.

Climate could influence mortality via its effects on agriculture and disease transmission. Overall, it has been found that sub-Saharan African countries with long lasting rainy seasons have lower mortality rates when compared to countries that have shorter wet seasons. Most likely this is due to the fact that longer wet seasons foster agriculture and hence food abundance.[38] In line with this interpretation we observed low mortality for all age groups in December and January, directly following the wet season. The increased mortality during the wet season has been mostly explained by an increase in gastrointestinal infections and malaria during that season.[8,9,39,40] Our findings in the research area are in line with these data. Prior examination of our group has indicated that guinea worm, schistosomiasis and malaria have a high prevalence at the end of the wet season and the transmission of malaria is highest at that time.[18,39] Compared to the dry season, the wet season shows increased parasitemia and severe anaemia rates in children.[41] Since children and older people are most susceptible to malaria, these factors possibly contribute to the excess mortality at the end of the wet season that we have observed.[40] Also, the incidence of gastrointestinal infections, skin infection and snake bites are higher during the wet season.[40]

The mortality peak during the wet season in September was driven by infectious diseases and affected children and older people alike. By contrast, mortality among older people showed a second peak during the dry season in April, due to non-infectious causes. The excess mortality for elderly could be partly explained by the harsh conditions at the end of this season, when food is limited and expensive, as reflected in the prices of crop and livestock.[23] This is however, not reflected in a higher mortality among children. Perhaps more important for older people, average temperature is highest at the end of the dry season in March and April. This will mostly affect older people with underlying cardiovascular diseases, that are especially prone for heat-associated mortality. During the epidemiologic transition in the area, infectious deceases are decreasing together with an increase in the prevalence of chronic diseases, and this could well be reflected by a change in patterns of seasonal variation in mortality. Hence, the peak in September is most likely to decrease, whereas mortality among older people at the end of the dry season in April will probably increase in the future. This reasoning is supported by the observation that the peak in April was more prominent in recent years.

The clustering of mortality over calendar time is in line with earlier findings in the research area, where we have described significant clustering of mortality, dependent on family and household characteristics, such as socioeconomic status.[42-45] Next to clustering on a geographical and family level we now show that mortality is clustering in time also.

We believe that studying whether mortality is seasonal and in what months we can expect excess mortality are relevant research questions, especially in such a rural environment with high infection pressure. Further insights in the seasonal variation in mortality in rural Ghana can be a first step towards better prevention and public health. We believe we have shown both, that mortality is seasonal and the effect size, or amount of excess mortality in specific months.

Several strengths and weaknesses of this study should be discussed. In a developing country with no available municipal registries, our longitudinal data set is a unique opportunity to study such a remote rural population. The verbal autopsy method is commonly used to assign causes of death in developing countries.[46,47] A limitation of our study is that we performed the verbal autopsy interviews in 2011 with a maximum recall period of eight years. Large variations in recall period could influence the data and it has hence been recommended that verbal autopsies should be performed only within two years after the deaths occurred.[48] However, in our data, the proportion of unspecified causes of deaths was not dependent on the recall period. This could be

partly explained by the fact that we only distinguished within the broader categories of infectious versus non-infectious causes of death. An additional explanation could be that since the majority of the people in the study area are farmers and the seasons are clearly linked to distinct agricultural activities, most do not have difficulty to recall the season of death. There was a moderate level of agreement between the adjudicating physicians, and between the original interviews and the re-interviews, which we have considered acceptable given the nature of verbal autopsies. A further limitation is that we lack precise data on fertility and migration rates. If fertility would have a seasonal pattern, this could be reflected in the variation in mortality as well. Migration will have especially influenced our results in young adults, as at this age individuals are most likely to move in and out of the area. It is less plausible that this has influenced child and old-age mortality.

All in all, this study shows that during the epidemiologic transition in tropical countries, mortality not only shifts from child mortality to old-age mortality, and from infectious to non-infectious causes of death, but that the distribution of deaths over the seasons probably changes as well. A better understanding of seasonal variation in mortality is of prime importance for public health policies.

Authors contributions

FE, UE, DvB and RW conceived the study; FE and UE designed the study protocol and collected data; FE and DvB performed the analysis and interpretation of these data. FE, JM and DvB drafted the manuscript; RW and UE critically revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

We have no competing interest.

Ethical approval

Ethical approval was given by the Ethical Review Committee of the Ghana Health Service, the Medical Ethical Committee of the Leiden University Medical Centre in Leiden, The Netherlands and by the local chiefs and elders of the research area.

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II

THE COMPRESSION OF MORTALITY AND MORBIDITY

Chapter 4

LIMITS TO THE COMPRESSION OF HUMAN MORTALITY

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Submitted

ABSTRACT

Experimental data suggest a limit to the compression of mortality based on the stochastic element in the ageing process. There is on-going debate whether in future mortality will be further compressed in humans. Here we have studied compression of mortality not only in relation to calendar time, but also, in relation to life expectancy to further elucidate the underlying process. We obtained life tables from Japan and the Netherlands, two countries that showed different trends in life expectancy from 1947 through 2008. As an indicator of mortality compression, we used the shortest age interval in which fifty percent of the annual mortality occurred (C50). In Japan and the Netherlands the C50 followed similar trajectories, only on a different time scale. We observed a limit to the compression of mortality in which fifty percent of annual mortality was compressed within an age band of 12 years in both countries, while life expectancy considerably improved. In accordance with genetic experimental data and in line with current theory on ageing, the observed limit to the compression of mortality is most probable determined by a residual variation due to the stochastic element in the rate of ageing between individuals.

INTRODUCTION

In countries that have undergone so-called demographic transition, mortality has shifted from younger to older ages, and the distribution of age-at-death has been compressed into a narrower interval, sometimes described as "rectangularization of the survival curve". [1,2] In a classic paper Fries (1980) was the first to define the concept of 'compression' of mortality and age-related morbidity, based on assuming a predetermined (and fixed) age-at-death. In other words, as individuals tended to live longer, deaths would become ever more crowded into a progressively later interval before the species-specific, fixed age-at-death.[3] However, Fries' assumptions have been overturned by subsequent progress in both demography and biology, providing fresh impetus for asking what is happening with respect to compression of morbidity.[4] Demographic observations indicate continuous increase in both average lifespan and the maximum age-at-death, whereas modern theory on ageing does not support a predetermined or fixed lifespan. [5] Instead, ageing is considered as an un-programmed process due to a stochastic accumulation of damage over time, the speed of which is dependent on both genetic and environmental determinants.[6,7] In this scenario, it is the accumulation of damage leading to the dysfunction of tissues and organs that explains the incremental risk of disease and disability, up to the moment that the amount of damage reaches a threshold that is no longer compatible with life.[8,9] Inherent to such damage accumulation, there will always be an individual variation in this stochastic process and therefore, the limit to the compression of old-age mortality will always be above zero. Moreover, this is in line with results from a classic genetic experiment in *Caenorhabditis elegans,* where the age-at-death distributions of a wilt-type population and an age-1 mutant population with an increased life span, were compared. In this experiment, the dispersion of mortality in the *age-1* mutant population expanded, but this was proportional to the increase in lifespan.[10]

The continuing debate about whether the human age-at-death distribution will be further compressed as the modal age-at-death increases is of fundamental as well as societal interest. In part, the situations remains unclear because various indicators have been used with contradictory results.[1,11-17] The standard deviation above the modal age-at-death (SD M+) is the most often used indicator of mortality compression, but it estimates compression of mortality *above* the modal age-at-death only, and thus merely in the oldest old. Out of the different indicators of mortality compression, Kannisto (2000) favoured C50, the shortest age-interval in which half of the annual mortality occurred, as the best, since it captures mortality compression on both sides of the modal

age-at-death.[16] A further limitation of previous studies on mortality compression was that they investigated compression of mortality over calendar time only.[1,11-17] Both life expectancy and mortality compression vary with annual fluctuations in the environment such as epidemics (especially influenza), economic and climatic changes. Hence, the study of mortality compression is incomplete when it is not related to the development of life expectancy.

Here, we studied the compression of the age-at-death distribution in Japan and the Netherlands, two countries with very different trajectories. Worldwide, life expectancy was highest in the Netherlands during the 1950's and 1960's. At the same time life expectancy in Japan was lagging far behind when compared to the Netherlands, but life expectancy in Japan subsequently showed an accelerated increase and then surpassed life expectancy in the Netherlands from the early eighties onwards. By comparing the mortality patterns in Japan and the Netherlands, we are able to disentangle the influences of calendar time and life expectancy on the compression of mortality. This provides further insight into the intrinsic process of mortality compression with important implications for future demographic and healthcare scenarios.

MATERIALS & METHODS

Data from Japan and the Netherlands were derived from the Human Mortality Database (HMD).[18] We used age-specific period mortality data from 1947 to 2008, with an age and year interval of 1x1.

To study the compression of mortality, we first calculated the modal age-at-death (M) according to Kannisto.[17] The age-specific deaths (d(x)) in the Human Mortality Database are recorded on an annual basis, and hence d(x) is given by the full year. However, since deaths are not equally distributed within a year, we have to calculate a more precise estimate according to the following formula:

$$M = x + \frac{[d(x) - d(x-1)]}{[d(x) - d(x-1)] + [d(x) - d(x+1)]}$$

Where *M* is the modal age-at-death, *x* is the age with the highest *d(x)* in late life and *d(x)* is the number of deaths between age *x* and *x + 1*.

We next calculated the shortest age interval in which fifty percent of the annual mortality occurred in a specific year (C50) as an indicator of the compression of mortality, according

to Kannisto. We used a total cohort of 100,000 and sorted the life table data by the d(x) in descending order and summed the d(x) values, starting with the highest value, until the total first exceeded 50,000. The number of years it takes to reach the total of 50,000 equals the shortest age interval in which fifty percent of mortality occurred in that year. Since we were interested in the compression of old-age mortality we only studied mortality compression above age 20, in order to exclude infant and child mortality. We hence summed up the d(x) values above age 20. As described earlier, d(x) is recorded in full years. Therefore, we first calculated the number of ages needed to reach a total of 50,000 after which we subtracted the fraction of the last added year that exceeds the specified total, in order to get a better estimate. A more detailed description of this method can be found in the publication by Kannisto.[16] To examine the trends of the C50 indicator over life expectancy, we calculated the C50 indicator for the years in which life expectancy was closest to 50, 55, 60, and so on.

In addition to the human data, we studied the compression of mortality in worm populations *of Caenorhabditis elegans* using data re-plotted by Kirkwood and Finch (2002) from an original experiment by Johnson (1990).[10,19] For these data we additionally calculated the relative C50, which is the C50 devised by the mean age-at-death.

RESULTS

Figure 1 shows the age-at-death distribution for Japanese and Dutch women from 1950 to 2008. In Japan after 1950, the initial decrease in early mortality was followed by a decrease in mortality at older ages, concomitant with a compression of the age-at-death distribution and a shift to increasingly higher ages. From 1950 to 2008, the modal age-at-death increased from age 75.1 in 1950 to 92.2 in 2008. Compared to Japan, the Netherlands in 1950 showed almost no early mortality and mortality at old age that was already compressed to a narrow age-interval. Between 1950 and 2008 in the Netherlands, the modal age-at-death increased from age 78.3 to 89.1.

We calculated C50 as an indicator of mortality compression. Figure 2 shows the C50 values for Japanese and Dutch women over calendar time from 1947 to 2008. In 1947, the C50 for women was 25.8 years in Japan and decreased to 12.0 years in 2008. In the Netherlands the C50 started at a lower level of 15.6 years and by 2008 it had decreased to 12.3 years for women. Apparently, the C50 approached a limit, in which fifty percent of annual mortality occurred within an age band of 12 years in both countries. In the Netherlands, this limit remained stable over the last fifty years.

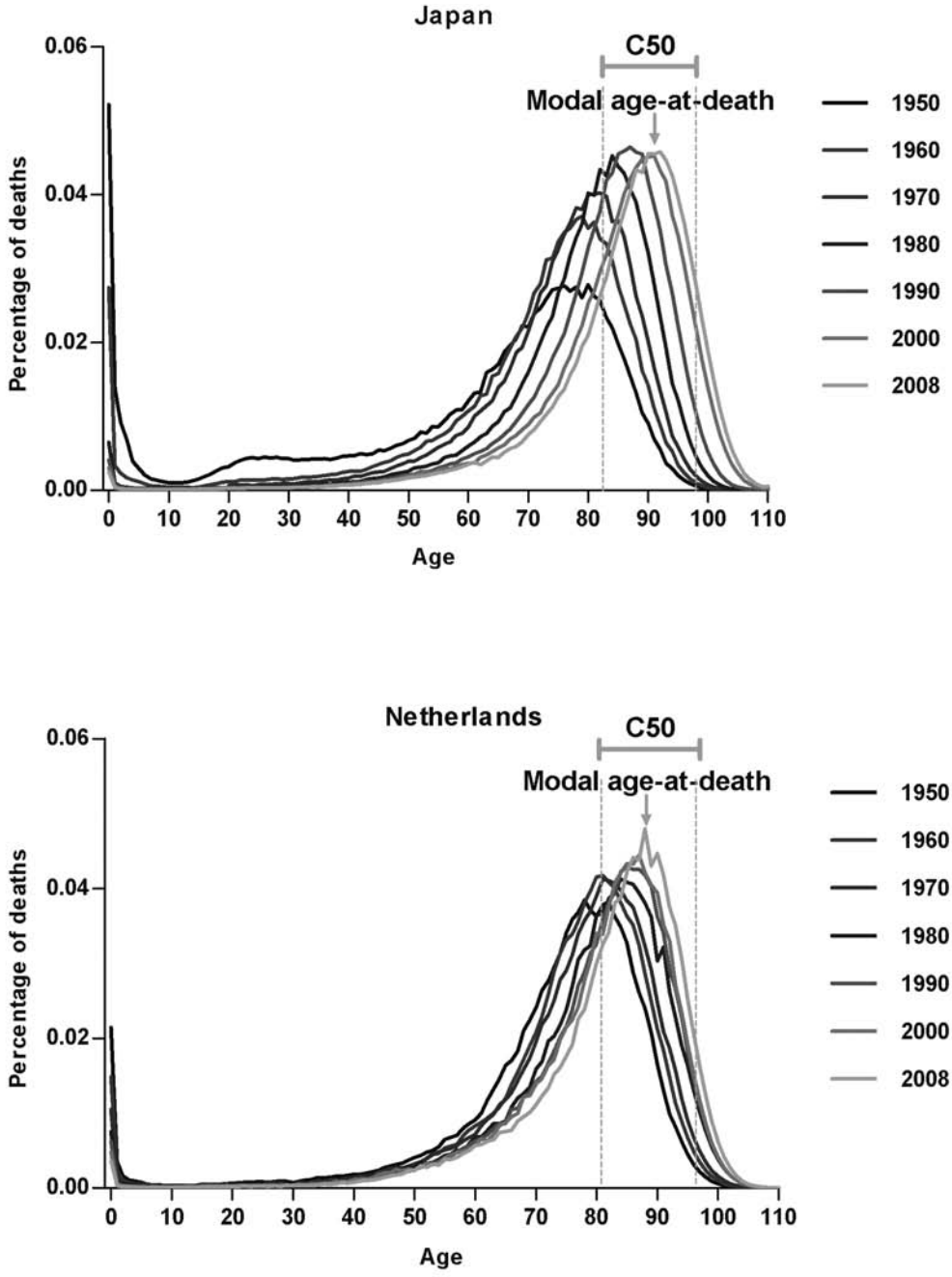

Figure 1. The annual age-at-death distribution of women in Japan and the Netherlands from 1950 to 2008, with additionally an illustration of the modal-age-at death and the C50 indicator of mortality compression

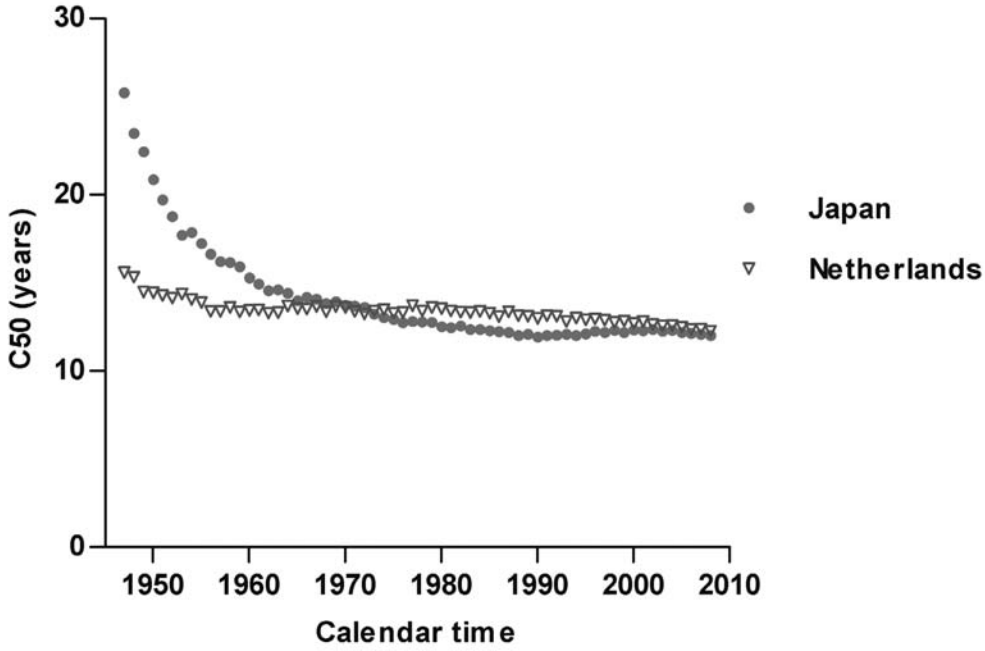

Figure 2. The compression of mortality, estimated by the shortest age interval in which fifty percent of the annual mortality occurred (C50), in relation to calendar time from 1947 to 2008.

Between 1947 and 2008 life expectancy of women increased from 53.7 to 86.0 years in Japan. For the Dutch, the corresponding life expectancy increased less, from 70.8 to 82.3 years. Since life expectancy for women in the Netherlands was already 70.8 years in 1947, we additionally calculated the C50 indicator for the Dutch women in earlier years, when life expectancy of the Dutch was similar to that of Japan in 1947. In the years 1896, 1907, 1922 and 1931 Dutch life expectancy first reached 50, 55, 60 and 65 years respectively. In figure 3 these additional estimates complete the historical development the C50 indicator over life expectancy in the Netherlands, and this shows that it practically overlaps with the trajectory of Japan.

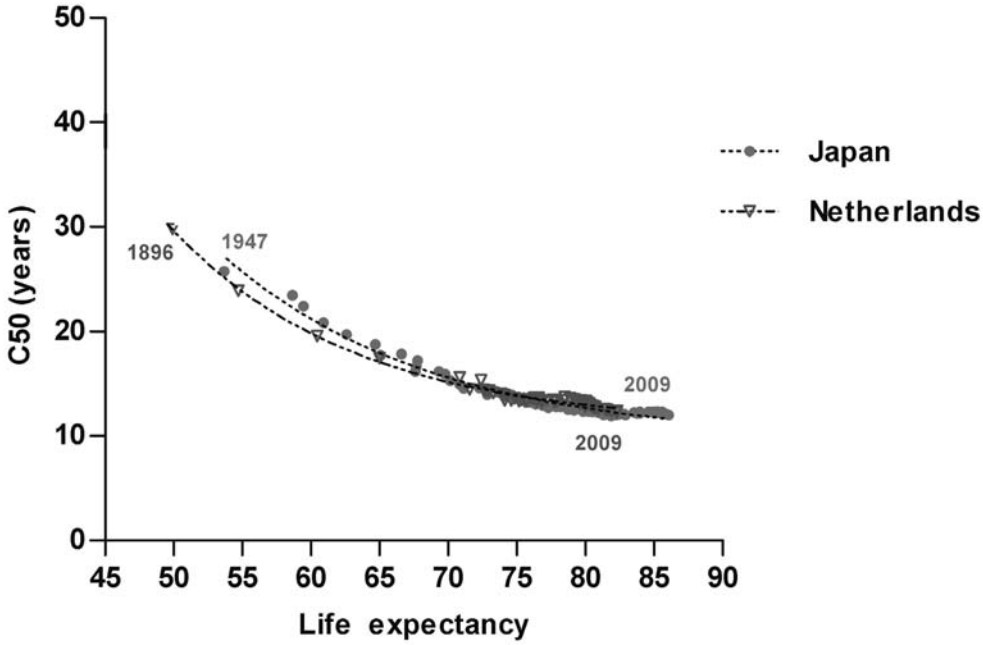

Figure 3. The compression of mortality, estimated by the shortest age interval in which fifty percent of the annual mortality occurred (C50), in relation to life expectancy in women of Japan and the Netherlands. For the Netherlands additional estimates are presented for the years 1896, 1907, 1922 and 1931, the years in which Dutch female life expectancy first reached 50, 55, 60 and 65 respectively.

In table 1 the C50 indicator is additionally summarized for men. In men the trends in mortality compression were alike when compared to women. The trajectories of C50 over calendar time are different between the two countries. However, when studying the C50 in relation to life expectancy, the trajectories of Japanese and Dutch males overlap as well.

Table 1. The shortest age interval in which fifty percent of the annual mortality occurs (C50) as an indicator of mortality compression, over calendar time and life expectancy for women and men in Japan and the Netherlands.

	Women C50 (years)		Men C50 (years)	
	Japan	Netherlands	Japan	Netherlands
Calendar time				
1950	20.9	14.4	21.7	15.7
1960	15.3	13.4	16.9	15.9
1970	13.7	13.6	15.6	16.9
1980	12.5	13.5	14.7	16.1
1990	11.9	13.0	14.5	15.1
2000	12.3	12.7	15.1	14.2
2008	12.0	12.3	14.9	13.6
Life expectancy				
50	25.8	28.2	27.6	28.9
55	23.5	23.9	25.1	22.8
60	20.9	19.6	20.6	19.6
65	17.7	18.4	17.4	17.2
70	15.3	15.6	15.6	16.5
75	13.7	13.4	14.6	15.5
80	12.3	13.4	14.9	14.7

In addition to the data for humans, we also examined distributions of individual life spans for two populations of the nematode *Caenorhabditis elegans*, one of wild-type and one carrying the life-extending *age-1* mutation. Table 2 shows the values of C50 and mean life span for each population as well as the equivalent values for Japan and the Netherlands in 1950 and 2008. Although there is a difference in mean life span between the two worm genotypes, and a corresponding increase in C50, the relative C50 values (C50/mean age-at-death) for the two genotypes are similar. The absolute and relative C50 in Japan and the Netherlands decrease over time. In both countries, the C50 values reaching similar levels in 2008.

Table 2. Values of C50, mean and relative C50 (C50/mean age-at-death) for two genotypes of the nematode Caenorhabditis elegans and for human population in Japan and the Netherlands in 1950 and 2008.

	Mean age-at-death	C50	Relative C50
Worm population	days	days	
Wild type	20.81	3.96	0.19
Age-1 mutant	36.27	6.99	0.19
Human population			
Japan	years	years	
1950	67.75	20.85	0.30
2008	85.73	12.15	0.14
The Netherlands	years	years	
1950	74.65	14.43	0.19
2008	82.26	12.27	0.15

DISCUSSION

We have found that the compression of the age-at-death distribution in Japan and the Netherlands followed identical patterns in relation to life expectancy. In both countries, the compression of mortality approached a limit with an age band of 12 years when life expectancy at birth was 80 years and over. This may indicate a future shift of the age-at-death distribution towards older ages without further compression. The analysis of compression of mortality in relation to calendar time yielded very different trajectories between the countries and was critically dependent on socioeconomic development.

It is still uncertain what factors determine this limit of compression. With the epidemiologic transition completed, the main causes of death have changed to ageing-related diseases.[20,21] Hence the present compression of mortality should be interpreted within a theoretical framework of ageing, where it is now generally accepted that the ageing process is not programmed, but rather the result of a stochastic accumulation of damage over time.[6,7,22-24] As the accumulation of damage has a stochastic element, there inherently always will be an inter-individual variation in the age at which the amount of damage reaches the threshold that is no longer compatible with life and it is this residual variation in the rate of ageing that is most likely behind the observed limit of old-age mortality compression.

It might be argued that a more genetically homogeneous population could explain for the observed compression of mortality, but it is unlikely that variation in the population genome in Japan and the Netherlands has significantly changed during the observation period. Moreover, even in a homogeneous population there is residual variation in the age-at-death distribution, as illustrated by data for the nematode worm *Caenorhabditis elegans*. Worm populations grown in laboratories have exceptional genetic uniformity and are cultured under highly uniform conditions, yet they show extensive variation in age-at-death of individual worms.[10] The increase in lifespan in the age-1 worms is usually interpreted as being the result of a slowing of the intrinsic ageing process, which means in turn that the intervals between the individual stochastic events that contributes to ageing become proportionately longer. It is this effect that most plausibly explains the increase in absolute C50 value, but the constancy in relative C50. For humans, we do not think there has been any underlying change in the speed of the ageing process (although this cannot be completely excluded as a minor contributor) so the gains in mean lifespan that have been made, combined with the reduction in C50 are likely to reflect postponement of some of the stochastic events from earlier to later ages within a relatively unchanged overall lifespan. Such an interpretation would be consistent with the idea that the age-associated stochastic events are partly from internal biochemical events and partly driven by environmental and/or lifestyle factors: the external events are postponed by the changes associated with demographic transition, while the internal changes are relatively less affected, although it must be acknowledged that such a distinction, in the absence of relevant data, remains hard to confirm.[7]

It remains to be elucidated whether, for humans, a homogeneous environment could further compress the age-at-death distribution. Smoking history for instance, highly increases mortality risks of individuals, and a high smoking prevalence can even cause a stagnation in life expectancy, as has been observed in the Netherlands.[25,26] Other environmental disparity exists in socioeconomic status, which is also known to be a strong determinant of mortality.[27] Within the Netherlands, one of the more egalitarian countries of the world, there is a seven year difference in life-expectancy between the poorest and the richest socioeconomic strata.[28] Closely related to socioeconomic status is the level of education. Higher levels of education are associated with stronger compression of mortality.[29] In both countries, the proportion of people with higher education has increased during the studied period.[30,31] It is likely that increased levels of education could have, in part, contributed to patterns of mortality compression that we have found. It cannot explain however, that the age interval in which fifty percent of the annual deaths occurs, has remained stable in the Netherlands for almost fifty years.

Furthermore, it has being argued that better prevention and improved (access to) health care are behind the prior observed mortality compression. In Japan a universal health insurance was introduced in 1961 and could have contributed to the compression of mortality in Japan.[32] If in former time only a small part of the population had easy access to health care, the introduction of a universal health insurance will have left the Japanese population more equal in terms of accessibility to health care, resulting in a compression of mortality over the last decades. In the Netherlands a sharp rise in life expectancy was observed in 2002, which has been attributed to improvements in health care for elderly, however, this has not further compressed the age-at-death distribution in the Netherlands[33] Overall, a uniform environment in terms of life-style, socioeconomic status, access to healthcare or other factors, is able to postpone morbidity and mortality to higher ages and hence increase the mean age-at-death, however it is unlikely that it will further compress the age-at-death distribution at old age, due to the stochastic nature of ageing.

It is a tempting idea that the compression of mortality that we have described, may also point to compression of morbidity. This should, however, be formally evaluated since the alternative scenario of decompression of morbidity is equally likely.[34,35] The explanation is that (fatal) complications of disease are prevented more effectively than the occurrence of disease per se.[35] Affluent lifestyles have resulted in an increasing burden of morbidity due to several chronic diseases, such as diabetes, atherosclerosis, cardiovascular disease and cancer, that more and more have become chronic diseases than a rapidly fatal disorders.[21] Further research on the evolution of patterns of morbidity is urgently needed to gain a full understanding of the implications of the changing mortality distributions for population health.

In conclusion, our observations in Japan and the Netherlands show a continuing shift of mortality to higher ages, together with a compression of the age-at-death distribution that appears to have reached a limit. This is in line with the current theory on ageing which is determined by a stochastic and uneven accumulation of damage over time, the speed of which determines the rate of ageing. It is the stochastic element in the process of ageing that defines the remaining individual difference in the age-at-death.

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Chapter 5

SEX DIFFERENCES IN HEALTHY LIFE EXPECTANCY IN THE NETHERLANDS

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ABSTRACT

For a long time, life expectancy at birth was used as the sole indicator of population health. More recently, population health is also being expressed as healthy life expectancy and it is debated how healthy life expectancy will develop in the future. Since it is known that men and women have very different health and disease trajectories, we compared healthy life expectancy between the sexes, at birth and at age 80. From 1985 to 2010 life expectancy at birth in the Netherlands increased from 73.1 to 78.8 for men and from 79.7 to 82.7 for women. During the same period, the expected number of years without disabilities and in good self-reported health increased parallel, pointing to a shift of disability towards older age. Paradoxically, however, there has been an expansion of morbidity per se, as indicated by a continuing decrease in life expectancy without chronic diseases from 51.4 to 47.2 for men and from 48.8 to 40.6 for women. After these diverging trends of the last thirty years, Dutch women nowadays have a life expectancy that is 3.9 years longer than men but a life expectancy without chronic diseases that is 6.6 years lower. When examining these figures in the oldest old, the number of years expected to live in good health is similar for the sexes, but women of 80 years can expect to live another 9.7 years, still almost two years longer than the 7.9 years for men. All in all, the increase of life expectancy in the Netherlands is accompanied by a shift of disability but an expansion of morbidity, which is much more pronounced in women. It remains to be examined what biological or social mechanisms are behind these large sex differences in healthy life expectancy in the Netherlands.

INTRODUCTION

In the last century, industrialized countries have gone through a demographic transition and showed a sharp increase in life expectancy at birth.[1,2] A major question is whether the additional years are spend in good health or in ill health. In the past decennia, it has therefore become practice to measure healthy life expectancy, which has been first introduced by Sullivan in the seventies.[3] Since the introduction there has been debate about how healthy life expectancy will develop in the future.[4-7] In this respect, it is important that men and women experience health and disease differently.[8,9] Healthy life expectancy trajectories, therefore, should be studied in the sexes separately.

Three general theories on the future of healthy life expectancy have been proposed. Gruenberg was the first who described the expansion of morbidity theory, where the increase in life expectancy would be accompanied with a decrease in healthy life expectancy due to a growing prevalence of chronic diseases.[10] Others later supported this sobering view, in which life expectancy, on the long term, would reach a plateau.[11-13] By contrast, Fries proposed the compression of morbidity, a more optimistic view proposing that diseases would be postponed to later in life, followed by a more or less sudden death.[14] In this scenario it was stated that with an increase in life expectancy, healthy life expectancy improves as well, at the end approaching life expectancy at birth. This was later supported by others who showed that an increase in life expectancy was not associated with a decrease in healthy life expectancy.[15] The third theory concerns the dynamic equilibrium status, where an increase in life expectancy would be combined with an expansion of mild disability, but also, with a decrease in severe disability and morbidity.[16] Several variants to these three main scenario's have been proposed.[17-19] It is still debated what scenario future life expectancy and healthy life expectancy will follow now that populations are ageing all over the globe.[20-22]

We studied the trajectories of healthy life expectancy in men and women from 1985 to 2010 in the Netherlands. We examined whether healthy life expectancy followed life expectancy at birth or whether the gap between the two further widened.
We compared the trajectories for the two sexes and, in addition, we studied how these trajectories have evolved in the oldest old. Further understanding of these trajectories is of prime importance as it has major implications for pensions, health care costs, and well-being.

MATERIALS & METHODS

Although there is consensus on how to calculate life expectancy at birth, there are many different ways to measure healthy life expectancy. The Dutch Centre for Statistics (CBS) uses three categories to measure healthy life expectancy: life expectancy without disabilities, life expectancy in good self-reported health, and life expectancy without chronic diseases.[23]

To establish the life expectancy without disabilities individuals aged 12 or above were questioned whether they were able to hear, see and move. Four categories were possible as an outcome on previous question: yes, with no trouble; yes, with some trouble; yes, with a lot of trouble; or no, not at all. Individuals responding with minimal one question: no, not at all; yes, with a lot of trouble; and yes, with some trouble were considered to have disabilities, either mild or severe. For the life expectancy in good self-reported health the following question has been asked: 'How is your health in general'? Responders answering with good or very good were considered to be in good self-reported health. Finally, for the life expectancy without chronic diseases a specific group of chronic diseases has been selected, from which it is known that they severely influence mortality or the quality of life. This selection contains: asthma/COPD, cardiovascular disease, CVA, hypertension, gastro-intestinal disorders, diabetes, backache, rheumatic disorders/ joint problems, migraine and cancer. Individuals having none of above listed diseases in the last 12 months were considered to have no chronic diseases. Questions concerning cardiovascular disease, CVA, hypertension and joint problems were only asked to individuals aged 12 years and over, with the assumption that those diseases do not occur below the age of 12.

We have included period data on life expectancy at birth and life expectancy at age 80 for the general Dutch population. The data were available annually from 1985 to 2010 for both sexes. [23]

RESULTS

First, we compared the traditional trajectories of life expectancy at birth in relation to the trajectories of healthy life expectancy in the Netherlands. The latter was divided into three categories: life expectancy without disabilities, life expectancy in good self-reported health, and life expectancy without chronic diseases. Figure 1 shows all four trajectories from 1985 to 2010, for both men and women.

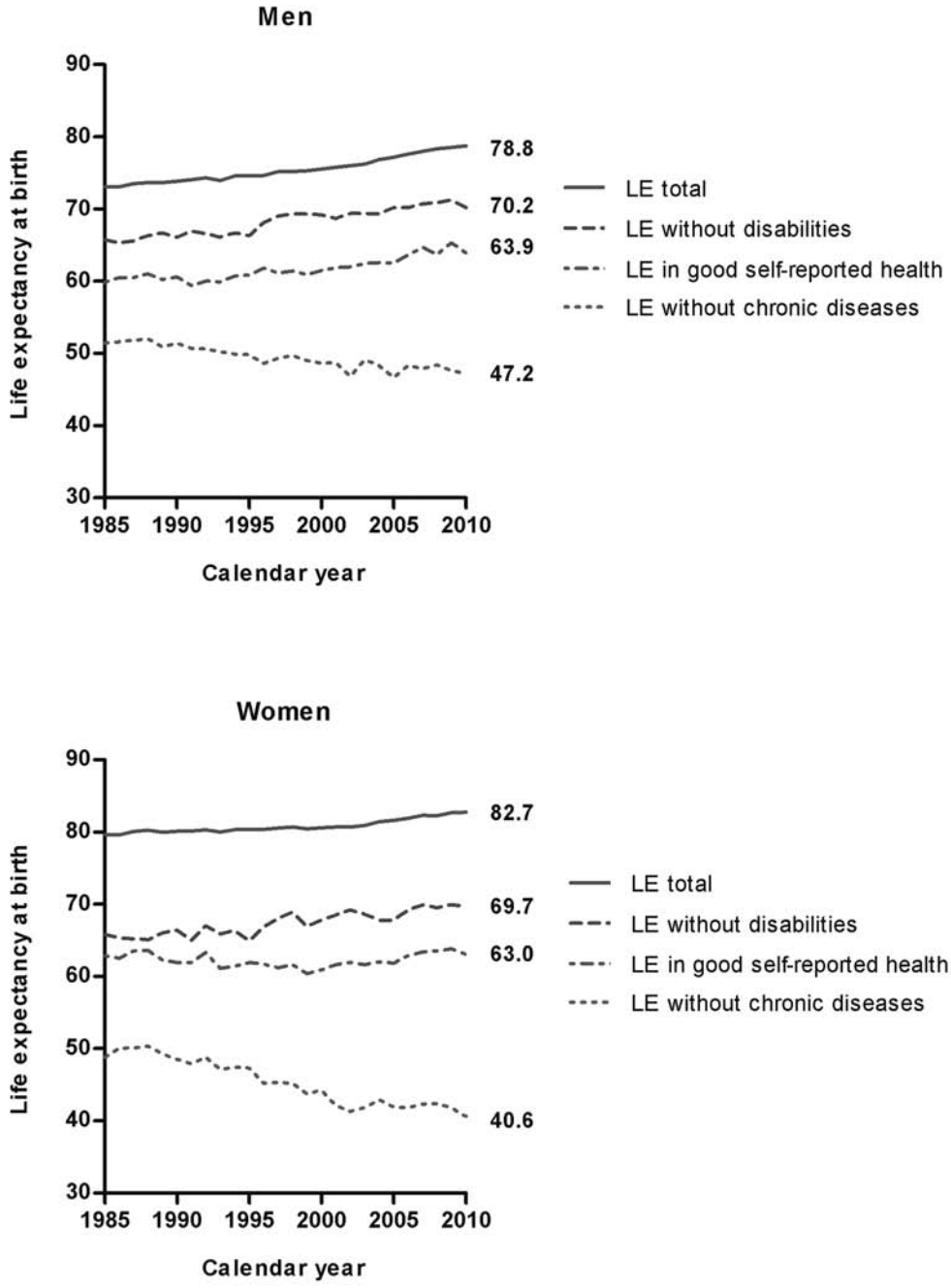

Figure 1. Trajectories of (healthy) life expectancy at birth from 1985-2010 in the Netherlands, for both men and women.

For men, life expectancy at birth increased by 5.7 years, from 73.1 to a total of 78.8 years in 2010. In addition, the three categories of healthy life expectancy developed in different ways. Life expectancy without disabilities and life expectancy in good self-reported health, both developed parallel to the life expectancy at birth and increased 4.5 years from 65.7 to 70.2 years and 4.1 years from 59.8 to 63.9 years respectively. By contrast, life expectancy without chronic diseases decreased during the studied time period. In 1985, life expectancy without chronic diseases in men was 51.4 years. By 2010 it had decreased 4.2 years to 47.6 years.

For women, total life expectancy at birth increased by 3.0 years from 79.7 to 82.7 years. Life expectancy without disabilities increased 3.9 years from 65.8 to 69.7 years. Life expectancy in good self-reported health increased 0.1 year from 62.9 to 63.0 years. In accordance with the observations in men, life expectancy without chronic diseases decreased, 8.2 years from 48.8 to 40.6 years. In 1985, women had a higher total life expectancy at birth, but their healthy life expectancy was similar to men. However, during the studied time period, men and women followed very different trajectories of life expectancy without chronic diseases. While for both sexes life expectancy without chronic diseases decreased, there was a much larger decrease in women compared to men, leading to women living 6.6 years shorter without chronic diseases compared to men.

In addition, we studied the trajectories of healthy life expectancy at age 80, shown in figure 2. For men, total life expectancy at age 80 and life expectancy without disabilities increased, respectively with 1.4 years from 6.5 to 7.9 years and 1.2 years from 3.0 to 4.2. There was only a marginal decrease in life expectancy in good self- reported health, which was 4.5 years in 1985 and 4.3 years in 2010. Life expectancy without chronic diseases decreased 0.3 years, from 1.6 to 1.3. For women, total life expectancy and life expectancy without disabilities, both increased; by 1.2 years from 8.5 to 9.7 years and 1.4 years from 3.0 to 4.4 years respectively. Life expectancy in good self-reported health and without chronic diseases decreased with 1.4 years from 5.6 to 4.2 years and 2.2 years from 3.8 to 1.6 years respectively. At age 80, women have a 2-year higher life expectancy, but they can expect to live the same number of years in good health, compared to men.

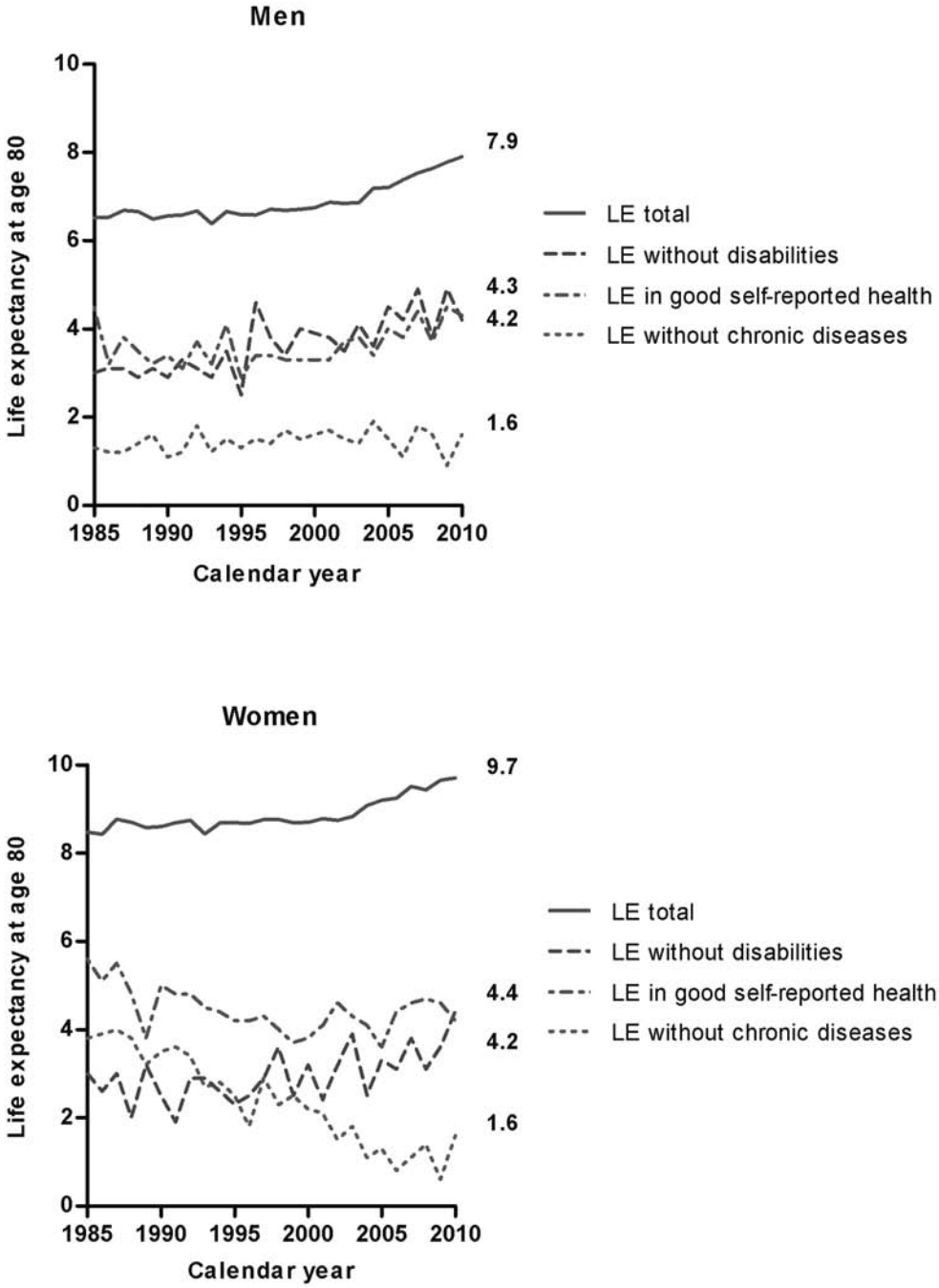

Figure 2. Trajectories of (healthy) life expectancy at age 80 from 1985-2010 in the Netherlands, for both men and women.

DISCUSSION

In the past decennia, the increase in life expectancy for both men and women in the Netherlands resulted in more years in good self-reported health and more years without disabilities. At the same time, an increasing number of years are lived with chronic diseases, indicating an expansion of morbidity. This last trend is observed in both sexes but is much more pronounced in women. There are two major explanations for this. First, it could be due to earlier diagnosis of diseases. Second, the prevalence of chronic disease, such as, cardiovascular disease and diabetes increased in the Dutch population during the studied time period.[24-26] This could also reflect changes in life style in this period. The extra years lived with chronic diseases (expansion of morbidity) however, do not necessarily suggest that we are becoming less healthy, since total life expectancy and disability free life expectancy increased. This suggests that early diagnosis and treatment postpone disabilities and increase our life expectancy. Several studies have also shown a relationship between the presence of chronic diseases during late adulthood and the manifestation of disabilities at older ages.[28-30]

Others have proposed a trade-off between increasing life expectancy and worsening population health.[11] The Dutch trajectories on healthy life expectancy at birth and in the oldest old, however, do not support this theory. Even at old age, the increase in life expectancy is not accompanied by an increase of disability. In accordance to other findings, life expectancy at old age temporally stagnated during the nineties in the Netherlands.[31] In 2002 this was followed by a sharp increase in life expectancy at old age, which is also present in our data.[32] Our results also show some contradictions with respect to other observations in the literature. Whereas some have found an expansion of disability in the Netherlands at advanced ages, we found a stable number of years with disability in both men and women, which persisted up to age 80.[33] Most probably this is due to a difference in the level of disability; mild disability increased, whereas severe disability reduced over time.[34,35] Only for women life expectancy in good self-reported health decreased in the oldest old. In a cohort of 85 years old Dutch women similar results have been found.[36]

During the last thirty years in the Netherlands, the gap between men and women in healthy life expectancy at birth has increased. In 1985, women had a higher life expectancy than men but the two sexes lived similar years in good health. Life expectancy without chronic diseases, however, decreased much more in women, leading to women having an almost seven years lower life expectancy without chronic diseases compared to men

in 2010. In the oldest old, women have a higher life expectancy, but life expectancy without chronic diseases is the same in men and women.

The sex difference in the proportion of years lived in good health, has also been observed in other countries and described as the male-female health-survival paradox.[37-40] Although women have a higher total life expectancy, men live longer in good health, which persists up to old age. The mechanisms behind this paradox are only partly known. The prevalence rates of musculoskeletal pain for example are higher for women compared to men, which has also been found in Dutch women.[41-43] In accordance, other observations from a study in multiple countries also showed that women have higher prevalence rates of non-lethal chronic diseases.[26] While the male-female health-survival paradox has further widened in the trajectories of life expectancy at birth, in the oldest old women have a similar healthy life expectancy than men in the Netherlands. This indicates that the sex difference in healthy life expectancy should be interpreted as an increased prevalence of chronic condition of middle-aged women.

All in all, our results show healthy life expectancy and total life expectancy at birth are continuously increasing for both men and women. However, more years are lived with disease which could reflect both early diagnosis and changed life styles. Sex differences in total life expectancy remain at old age, but men and women can expect a similar number of years of healthy life expectancy at age 80. At the end of life there remains a period of frailty that can be postponed, but not further compressed. Hence, the need for care will be concentrated at the end of life. From an economic perspective, this indicates that the highest costs will not increase with the increase in life expectancy and will be fixed at a period at the end of life, which is in line with earlier studies.[44,45] This is of prime importance as it has major implications for pensions, health care costs, and well-being. What biological or social mechanisms are behind the striking sex-difference in healthy life expectancy in the Netherlands remains to be examined.

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Chapter 6

BETTER HEALTH, LONGER LIVES

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Life expectancy has steadily increased with around 2.5 years per decade over the past 150 years and continuous to do so at a similar rate.[1] Before 1950, the increase in life expectancy was primarily driven by reductions in child mortality. During the last decades, however, the increase in life expectancy is mainly the result of mortality reductions at old age.[2] Better living conditions and hygiene have saved us from an early death, while incremental health care innovations have brought us an old age.

When confronted with the increasing life expectancy, individuals are uncertain whether they would like to live longer than the nowadays average of 80 years. In sharp contrast almost everybody prefers to maintain a good health when growing old. This notion is even more pertinent as not only life expectancy has greatly increased, but the prevalence of life-style related diseases such as cardiovascular disease, obesity and diabetes as also increased.[3] It seems, that the increase in longevity comes at a cost of ill health. Here however, we reason that this conclusion is unjust and that we live longer in better health. To unravel this paradox, we should not only consider life expectancy with and without chronic diseases, but also life expectancy with and without disabilities, and life expectancy in self-perceived health.

For several decades in the Netherlands, life expectancy without disability and life expectancy in good self-perceived health have increased parallel to the increase in life expectancy.[4] During the same period life expectancy without chronic diseases has decreased, in line with the international trends. There is a sound logic that the reduction of years without chronic diseases can coincide with living in better health for longer. First, changes in life-style have increased the prevalence of hypertension, obesity, diabetes and other life-style related diseases. Second, ailments associated with ageing are diagnosed earlier due to increased health awareness and screening. But third, treatment outcomes of disease states are ever improving and permanent damage is increasingly being prevented. The net result is that life-style changes and earlier diagnosing have contributed to an increased number of years 'suffering' from chronic diseases, but at the same time appropriate treatment of these ailments provided us with an extra number of years without disabilities. We now live healthier for longer than ever before.

Some have a more pessimistic view and argue that longer lives bring with it worsening health.[5] This is an often-made misinterpretation when looking at trajectories of the number of years with and without chronic diseases only. Being diagnosed with disease by the doctor is not the same as being disabled. To illustrate this stand, we take hypertension as an example, the occurrence of which has greatly increased over the last decades. With

improved screening algorithms for hypertension, we managed to reveal the ailment, to treat it and to delay the occurrence of cardiovascular disease. By preventing stroke and heart failure at an early age, disability and death are postponed to a higher age. When diagnosed with hypertension, one is labelled as being diseased but it allows for adequate intervention. As a result of our impetus, life expectancy in good self-perceived health is still on the increase.

One thing that should be noted is that there is a considerable female-male difference in morbidity, which has been observed in various countries and persists up to old age. [4] Although women have higher life expectancy than men, they proportionally live more years in ill health. There is little known about the exact mechanisms behind this sex difference. It is partly explained by differences in the prevalence of non-lethal chronic conditions. Women for instance suffer more from osteoporosis and musculoskeletal disorders. Furthermore, it has been argued that women have a shorter 'patient delay', are more rapidly seeking medical attention and are consequently diagnosed with disease earlier than men.

It is a daunting task to predict the shape of health and disease trajectories in the future, but past performance in healthy life expectancy allows some probabilistic conclusions. People born today, will survive up to very old age while maintaining a good self-perceived health. This has important implications for society. One of the fears of our ageing populations is that this fuels an explosion of health care expenditures. The highest costs appear at the end of life, to accommodate disability and frailty, but as the data show, this number of years is not likely to expand. At the end of life there will remain a period of frailty that cannot be further compressed, but is delayed to later age. It is a well-known fact among health economists that the increase in expenditures is primarily driven by health care innovations.

It is a privilege to live in a society where so many people live up to old age and never before have we enjoyed so many years without disability that are well perceived. Some argue that this longevity revolution becomes untenable, as social and pension systems will fail. The new insight is that the extra years that we have gained are good years and need to be exploited. It allows people to stay active and be vital for a longer period of their life course. It is a challenge to rearrange our societies in such a way that older people can contribute and participate for longer. Postponing pension age, for example, can help to accommodate the labour shortage that is projected and will reduce the burden on the pension systems.[6]

It is time people realise that they can foresee a healthier and longer life and plan their life course accordingly.

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III

THE PLASTICITY OF OLD-AGE MORTALITY

Chapter 7

MALLEABILITY OF HUMAN AGEING: THE CURIOUS CASE OF OLD-AGE MORTALITY IN JAPAN

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ABSTRACT

Steady growth in human life expectancy has been a key feature of the last century, with projected further increases likely to have enormous impacts on societies world-wide. Despite the significance of these changes, our understanding of the factors shaping this trend is incomplete. During most of the historical increase, by far the major influence was progressive decline in early and mid-life death rates, due to reduction in premature deaths, caused chiefly by infection. Recent decades have seen the emergence of a new driver of increasing longevity – declining mortality among those who are old already, pointing to greater malleability in human ageing than had been foreseen. There is still debate, however, how much of this decrease in old-age mortality is due to a better early-life environment and how much due to improved conditions in late life. A unique resource exists in the case of Japan, where material circumstances for the general population were consistently adverse through the early decades of the 20th century, but improved rapidly after 1950. Here we compare the Japanese birth cohorts of 1900, 1910 and 1920 and follow their period and cohort mortality trends. The results show that cohorts with similar environments early in life have very different mortality trajectories in old age. This strengthens the expectation that preventive measures in later life can deliver great benefit, while not contradicting the importance of life course approaches to improving health and wellbeing.

INTRODUCTION

Over the last century mortality in developed countries has decreased at all ages.[1-3] Initially, the largest decrease was in child mortality and only in recent decades has the decrease been predominantly at old age.[4,5] The determinants of the decrease in child mortality are well known, and include improved hygiene, vaccinations and other preventive measures. Exposures to infectious diseases and to poor nutrition early in life, including the period *in utero*, have been linked with mortality in old age.[6-11] In the unusual case of individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944-45, when for about six months average daily adult intake was reduced to around 700 kcals, persistent epigenetic differences have been detected six decades later.[12] Individuals exposed peri-conceptionally to famine displayed, in their sixties, significantly less DNA methylation of the imprinted *IGF2* gene that is involved in human growth and development. In this accident of history the timing of the nutritional stress could be determined with precision, and it is striking that individuals similarly exposed to the famine but during late gestation, did not show persistent epigenetic differences. While the evidence that developmental and early-life events can influence long-term health in rodents and humans is incontrovertible,[13-16] much remains to be learnt about the extent and scale of such effects within the broader context of increasing human life expectancy. Furthermore, intervention strategies based solely on targeting developmental factors are of little use to the growing numbers of older adults.

Establishing the contribution of factors acting directly on mortality in later life is challenging. In most countries, improvements in living conditions have occurred relatively smoothly over time, so that the cohorts now reaching old age will have benefited from changes that have occurred throughout the life course. There are, however, instances where changes have been more sudden. A study of changes in old-age mortality in East Germany after reunification with West Germany has shown rapid convergence of death rates in the two populations, rates in the East falling within little more than two decades to match those in the West.[17,18] However, this was only seen at very high age, when mortality rates always converge, and there is still some who argue that old-age mortality is biologically fixed.[19-21] Data from smoking cessation in old age does suggest, however, that health benefits can still be achieved, even when the anti-smoking intervention was introduced in old age.[22]

A striking instance of transition to a long-living population structure is seen in Japan, which in recent years has led the world in life expectancy. Although many countries that

experienced development through the 20th century have witnessed some features of the same transition, the case of Japan is exceptional because of the relative uniformity of living conditions for the general population during the first half of the 20th century, as evidenced by mortality statistics, followed by the rapid pace of improvements after 1950. Aspects of Japanese longevity are notably different from that in other countries, specifically the relatively small range of socioeconomic differences and the greater prominence of stroke as compared to heart disease.[23] Nevertheless, Japan provides an intriguing "natural experiment" to examine impacts of health improvements at different stages in the life course which can reasonably be expected to have general relevance for the broader biology of human ageing and longevity.

MATERIALS & METHODS

We used Japanese period and cohort mortality data for the study. Period mortality data and cause-specific mortality data were retrieved from the publicly available 'Historical Statistics of Japan' of the Japanese Ministry of Health, Labour and Welfare. Period mortality data were accessible for the years 1899-1903, 1909-1913, and 1921-1925, with a 1x5 age-year interval. We employed these mortality data as an approximation to 1900, 1910 and 1920 period mortality data. We recognized issues on these official mortality data and studies revising these mortality data, notably by Mizushima.[24] However, the patterns of revised age-specific mortality rates were not significantly different from the official mortality data when three periods were compared. The cohort mortality data were obtained from a study conducted by Nanjo and Yoshinaga,[25] and were available with a 1x1 age-year interval.

All calculations were performed on publicly available population data. No participants were recruited for this study. Ethical approval was therefore not considered necessary to study population mortality and morbidity statistics.

RESULTS

Figure 1 shows age-specific period and cohort mortality rates for the Japanese birth cohorts of 1900, 1910 and 1920, using publicly available data from the Historical Studies of Japan (Japan, 2011). Looking at period mortality, the profiles in 1900, 1910 and 1920 were almost identical for all age categories.

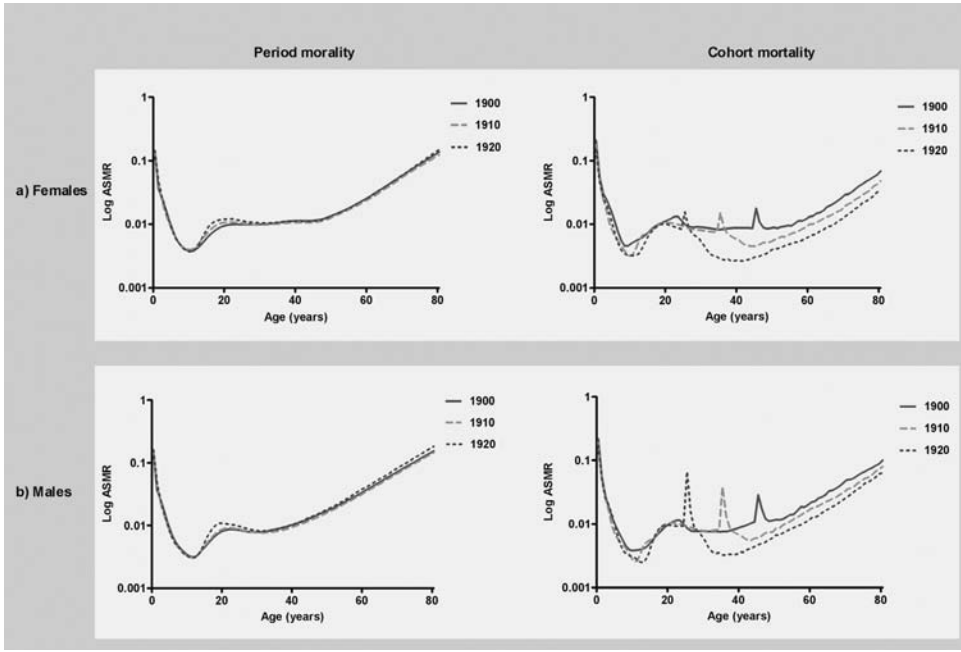

Figure 1. Period and cohort annual mortality rates for a) females and b) males. ASMR denotes Age-Specific Mortality Rate.

We can thus use these data to compare period and cohort mortality rates of three populations that were similarly exposed to an adverse environment early in life and which began to experience a rapidly improving environment at age 30, 40 and 50 years of age, respectively. These three birth cohorts had similar mortality rates at younger ages, only around the age of 10 years the mortality in 1910 and 1920 was lower compared to 1900. The trends started to follow complete separate trajectories at middle age as conditions improved, and these differences persisted into old age. On closer observation, the 1920 birth cohort showed a mortality peak around the age of 25 years due to World War II, followed by a subsequent decrease of mortality before a steady increase with age. The 1910 and 1900 birth cohorts showed similar patterns, with war-related mortality peaks around ages 35 and 45, respectively.

To study further the mortality differences at middle and old age as found in the cohort mortality data, we plotted the differences in cohort mortality rates of the 1910 and 1920 cohorts compared to the mortality rates of the 1900 cohort, shown in Figure 2.

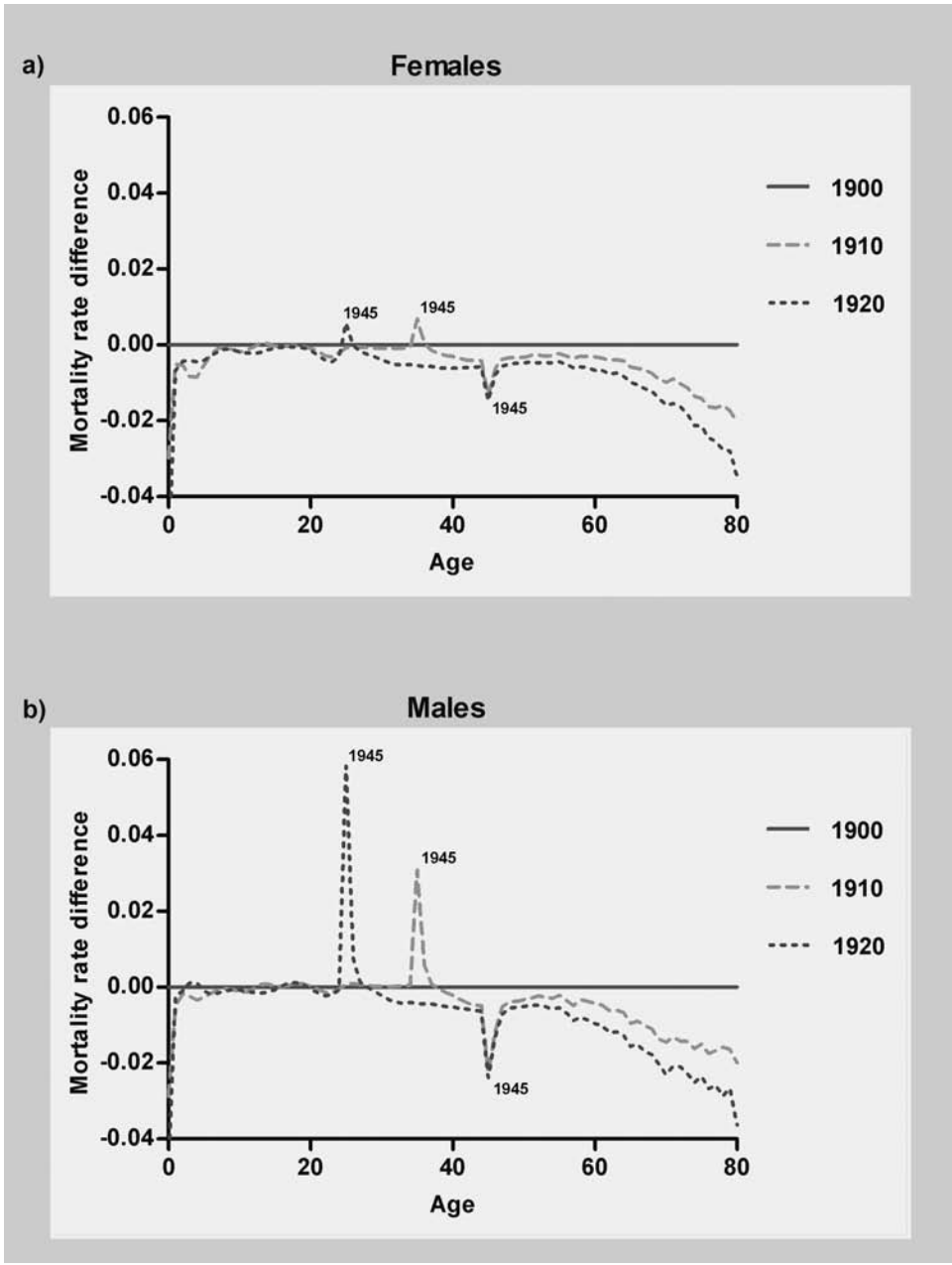

Figure 2. Cohort mortality rate differences of the 1910 and 1920 birth cohorts when compared to the 1900 birth cohort, for a) females and b) males.

With exception of infant mortality (age 0), the mortality rates of the 1910 and 1920 birth cohorts were very similar to the mortality rates of the 1900 cohort at younger ages, for both females and males. However, from 1950 onwards, with the improvement of the environment after the war, the mortality rates were considerably lower for the more recent birth cohorts. For the 1910 cohort, the mortality difference started at age 40 and persisted up to old age. The 1920 birth cohort started to diverge at age 30 and shows the strongest mortality decrease at old age.

In addition to the all-cause mortality data, it is important to consider changes in causes of death. Table 1 presents the cause-specific death rates of the age group 65-75 years for the periods 1965-1974, 1975-1984 and 1985-1994, respectively, corresponding to the cohorts born in 1900, 1910 and 1920. For individuals born in 1920, most cause-specific death rates (cerebrovascular disease, heart disease, tuberculosis, peptic ulcer, accidents and suicides) were lower than in the 1900 birth cohort. The reduction in mortality was most pronounced for deaths due to cerebrovascular disease. Only the mortality rates due to smoking-related malignancies (trachea, bronchus and lung) were higher for the 1920 cohort. Nevertheless the overall mortality of malignancies was lower for the 1920 birth cohort.

Table 1. Cause-specific mortality rates at age 65-75 years

Causes of death	1900 cohort	1910 cohort	1920 cohort
Cerebrovascular disease	1142	610	277
Heart disease*	464	411	314
Malignant neoplasm	744	719	688
Smoking related**	86	152	141
All other	658	567	547
Tuberculosis	86	33	11
Peptic ulcer	47	21	8
Accidents	84	59	58
Suicides	44	39	29

Mortality rates are per 100,000 per year, * including hypertension, **trachea, bronchus and lung.

Table 1 is generated from cause-specific mortality rates for the birth cohorts born in 1900, 1910 and 1920 at the age of 65 to 75 years. Consequently it consists of period mortality data from 1965-1974, 1975-1984 and 1985-1994, for the 1900, 1910 and 1920 cohorts respectively. The cause-specific death rates were calculated per 100,000 persons per year, by dividing the total number of deaths due to a specific cause, by the population size of that age group in that year and then multiplied by 100,000.

DISCUSSION

Our analysis of these Japanese data reveals that cohorts with similar environmental conditions early in life had very different old-age mortality trajectories, when exposed to environmental improvements at middle age. Mortality of the 1920 cohort was significantly lower compared to the cohorts from 1900 and 1910. This difference was mainly due to large reductions in cerebrovascular disease, which was the major cause of death in Japan. These findings strongly suggest that a large part of the mortality benefit is through old-age plasticity supporting growing recognition of the malleability of human ageing.[27] The contrary view – that old-age mortality is essentially fixed – is still held, however, and underlies, for example, the concept of "compression of morbidity" which suggests that the goal of age-related medicine should be to postpone as far as possible the onset of diseases within the fixed human lifespan,[28] at least until such time as science can slow down the ageing process itself.[20,21,29-31]

In view of the scale of the societal impacts of increasing human life expectancy, it remains important to establish the mechanisms that underlie the ongoing declines in death rates at the oldest ages, which in general show associations both at international level with wealth as measured by gross domestic product[32] and intra-nationally with socioeconomic status.[33] In Japan it is clear that socioeconomic conditions improved rapidly after 1950, but the 'proximate' causes that mediate between wealth and health in reducing mortality are less clear. One possibility is simply that better medical care interventions became available, as in the example of cardiovascular disease management.[34] Improvements in healthcare could explain the found reduction in cerebrovascular disease, which has been suggested by others as well.[23] The potential importance of medical care to falling mortality is, however, commonly over-stated.[35] Additionally, in the case of Japan, a significant step in reducing social inequalities was the introduction of the universal coverage of health insurance in 1961.[36] It can be argued that more universal access to existing medical care and preventive interventions may have played a part.

An alternative possibility is that improved living conditions act systematically on the array of factors that either exacerbate or improve the progressive accumulation of various forms of damage. That is, the improvement might arise not because diseases are treated better or more universally, but because diseases themselves progress more slowly, or are ameliorated by improved general conditions. For example, many deaths attributed to heart disease and stroke can be identified as proximate consequences of cold exposure

in winter.[37] Amelioration of cold exposures with improving social conditions may thus have an impact upon many specific causes of death, without any change in the classical risk factors or treatments of those specific causes. Older people also suffer extensive co-morbidity – for example in one detailed study of a 1921 birth cohort of 85-year olds in Newcastle-upon-Tyne, the majority of participants had between 4 and 6 age-related diseases.[38] It would not be at all surprising to see environmental and social improvements impacting upon several or all such co-morbidities simultaneously.

Finally, it is possible that a general improvement in environment, living conditions and social wellbeing might impact upon the accumulation of molecular and cellular damage that is thought to constitute the intrinsic ageing process.[39] That is, ageing itself might be slowed from different ages in the different cohorts considered. Such an explanation, which involves the diverse effects of nutrition, lifestyle, occupation etc. interacting with biochemical stresses and repair mechanisms could be compatible with the strong socioeconomic gradients seen in health and life expectancy. However, although not undisputed,[40,41] it is considered that the slope of log mortality rates is an indicator of the population rate of ageing,[42] and it should be noted that the progressive reductions of risk between the cohorts reported here bring about either a parallel reduction or a small increase in the gradient of the log-mortality slope.

In conclusion, cohorts with similar early life environments have very different mortality trajectories in old age, indicating that old-age mortality is much more malleable than commonly thought. This strengthens the expectation that interventions in later life, which include lifestyle (especially exercise), nutrition and proactive health screening with preventive medical treatments such as statins and control of moderate hypertension, can deliver great benefit.

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Chapter 8

A RETROSPECTIVE COHORT ANALYSIS OF MORTALITY IN FORMER OLYMPIC ATHLETES

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ABSTRACT

Objective: Physical exercise associates with lower mortality risk and is thus recommended by public health organisations all over the world. High intense exercise also places great strain on the body and these detrimental effects could counterbalance the health benefit.
Design: Retrospective cohort study in former Olympic athletes for all cause mortality.
Participants: We included 9,889 athletes who participated in the Olympic Games from 1896 to 1936, representing 43 types of disciplines with different levels of cardiovascular, static and dynamic intensity exercise, high or low risk of bodily collision, and different levels of physical contact.
Results: Hazard ratios (HR) for mortality among athletes from disciplines with moderate cardiovascular intensity (HR 1.01, 95% confidence interval [95% CI]: 0.96 to 1.07) or high cardiovascular intensity (HR 0.98, 95% CI: 0.92 to 1.04) were similar when compared to athletes from disciplines with low cardiovascular intensity. The underlying static and dynamic components in exercise intensity revealed similar non-significant results. We did observe increased mortality among athletes from disciplines with a high risk of bodily collision (HR 1.11, 95% CI: 1.06 to 1.15) and with high levels of physical contact (HR 1.16, 95% CI: 1.11 to 1.22). In a multivariate analysis, the effect of high cardiovascular intensity remained similar (HR 1.05, 95% CI: 0.89-1.25). The increased mortality associated with high physical contact persisted (HR 1.13, 95% CI: 1.06-1.21), however, bodily collision became non-significant (HR 1.03, 95% CI: 0.98-1.09), as a consequence of its close relationship with physical contact.
Conclusions: Among former Olympic athletes, engaging in disciplines with high intensity exercise did not bring a survival benefit when compared to disciplines with low intensive exercise. Those who engaged in disciplines with high levels of physical contact suffered an increased mortality later in life.

INTRODUCTION

Public health associations recommend physical exercise since it is associated, amongst others, with lower mortality risks, better mood and cognition, and lower prevalence of cardiovascular disease.[1-7] However, when Pheidippides ran from Marathon to Athens in 490 BC to announce the Greek victory on the Persians, he died on arrival. As his case illustrates, exercise of high intensity can also place great strain on the body and can cause serious injuries and damages.[8] Key is whether regular high intensity exercise is associated with lower or higher mortality risk. When the first modern Olympic Games were held in Athens in 1896, including a marathon run to Athens, it was decided to shorten the distance with the death of Pheidippides in mind. The nowadays distance of 42 kilometres and 195 meters was only later determined during the third Olympics in London, when the royal family requested to extent the run from the start at Windsor Castle to the royal stage in the White City Stadion. This year the Olympic Games were back in London again, but it is still debated whether high intensive exercise, as in many Olympic disciplines, is beneficial for reducing mortality risk.[9-10]

The effect of high intensive exercise on mortality later in life has mostly been studied among professional athletes, using the general population as a control group. The outcomes from these studies differ; some did not find a survival benefit, whereas others, showed lower mortality in athletes than in their non-athletic counterparts from the general population.[11-24] It is well possible that the lower mortality risk of professional athletes is due to specific social and psychometric characteristics and it remains to be elucidated whether for athletes, high intensive exercise brings a survival benefit or an increased mortality risk.

Here we have analyzed mortality patterns in a large historic cohort of athletes who had all participated in the Olympic Games from 1896 to 1936 but performed at different levels of cardiovascular, static and dynamic intensity exercise.

Materials & Methods

Study population

In May 2011, we retrieved a cohort of 21,127 former Olympic athletes from the online Sports Reference Database, the largest online database with Olympic athletes, which is continuously updated.[25] Figure 1 summarizes the inclusion process in a flow diagram. We included 9,889 former Olympic athletes, born between 1830 and 1910 with a known age-at-death, who participated in at least one of the Summer Olympic Games between 1896 and 1936. We excluded 2,162 athletes from nine disciplines that were not mentioned in the classification of the American College of Cardiology.[26] We classified skeleton as bobsledding and polo as equestrian, due to very similar types of exercise. From 7,534 athletes the age-at-death was unknown due to either an unknown date of birth and/or date of death. Finally we excluded 1,542 participants born after 1910, since athletes born afterwards could possibly be still alive.

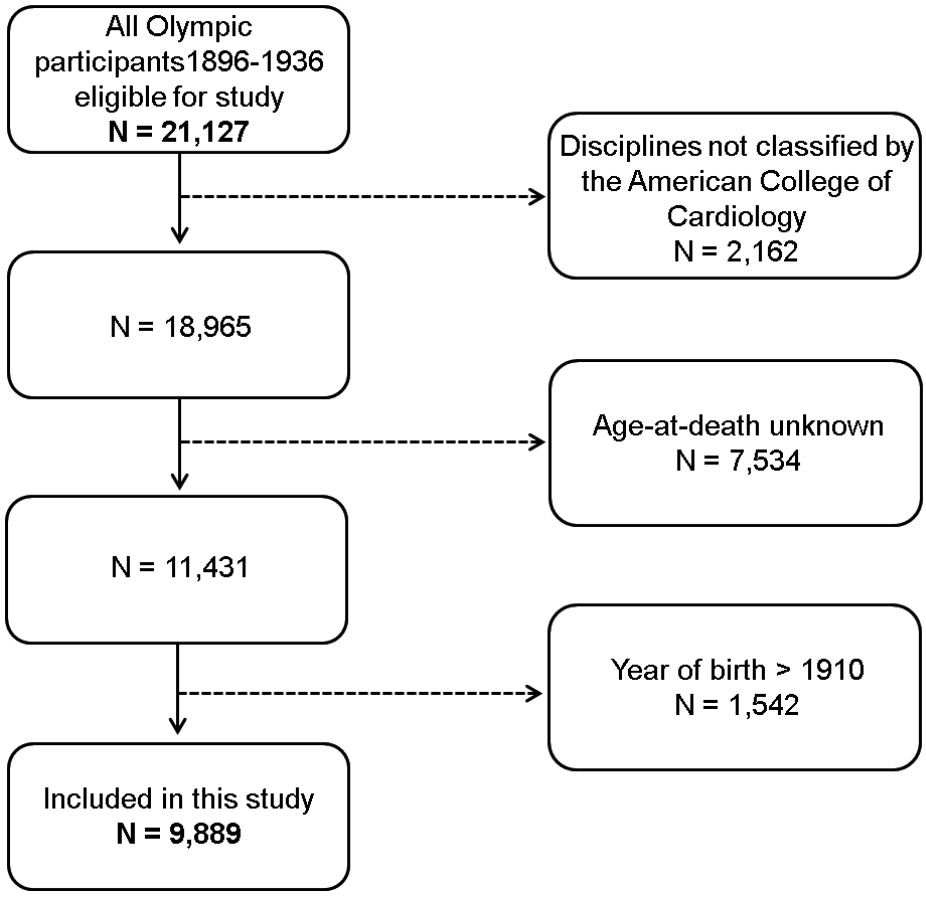

Figure 1. Flow diagram illustrating the inclusion of former Olympic athletes in the study.

Classification of Olympic disciplines

The 43 Olympic disciplines were classified according to the classification system of the '8th Task force on the classification of sports' by the American College of Cardiology.[26] Classification of the cardiovascular intensity sums a static component reflecting maximal voluntary muscle contraction, and a dynamic component reflecting maximal oxygen uptake and both were categorized at three levels of intensity: low, moderate and high. They also defined three levels of static and dynamic intensity: low, moderate, and high. When an athlete had participated in multiple disciplines, we categorized him/her in the discipline with the highest cardiovascular score. The risk of bodily collision was classified also, by the American College of Cardiology.[26] Finally, we have classified the various disciplines as low (non-contact), moderate (limited-contact) and high (full-contact) sports, according to the classification of contact sports of the American Academy of Paediatrics.[27] The levels of exercise intensity were similar in athletes who were included and excluded in the present analysis (data not shown).

Statistical analysis

We have calculated hazard ratios for all cause mortality using a left-truncated Cox proportional hazards model entering participants at the age of first participation in the Olympic Games. All analyses were adjusted for sex, year of birth and nationality. Calculations were performed with Stata 11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

RESULTS

We included 9,889 athletes from 43 different Olympic disciplines that were classified in various categories of intensity of exercise, risk of bodily collision, and the level of physical contact. Table 1 summarizes the characteristics of these 43 Olympic disciplines. In addition, figure 2 shows all 43 disciplines stratified for the level of static, dynamic and cardiovascular intensity, classified according the American College of Cardiology.[26]

Table 1. Characteristics of 9,889 athletes from the 43 Olympic disciplines.

Discipline	N (%)	Cardio-vascular Intensity*	Static in-tensity*	Dynamic Intensity*	Risk of bodily collision*	Physical contact**
Alpine Skiing	27 (0.3%)	High	High	Moderate	Yes	High
Archery	66 (0.7%)	Low	Moderate	Low	No	Low
Basketball	26 (0.3%)	High	Moderate	High	Yes	High
Biathlon	8 (0.1%)	Moderate	Low	High	No	Moderate
Bobsledding	91 (0.9%)	Moderate	High	Low	Yes	Moderate
Boxing	277 (2.8%)	High	High	High	Yes	High
Canoeing	28 (0.3%)	High	High	High	No	Low
Cricket	14 (0.1%)	Low	Low	Low	No	Moderate
Cross-country skiing	152 (1.5%)	Moderate	Low	High	No	Moderate
Curling	12 (0.1%)	Low	Low	Low	No	Low
Cycling	388 (3.9%)	High	High	High	Yes	Moderate
Decathlon (athletics)	86 (0.9%)	High	High	High	No	Moderate
Diving	157 (1.6%)	Low	Moderate	Low	Yes	High
Equestrian	315 (3.2%)	Low	Moderate	Low	Yes	Moderate
Fencing	561 (5.7%)	Low	Low	Moderate	No	Moderate
Field Hockey	159 (1.6%)	Moderate	Low	High	Yes	High
Figure Skating	90 (0.9%)	Moderate	Moderate	Moderate	No	Moderate
Golf	65 (0.7%)	Low	Low	Low	No	Low
Gymnastics	687 (6.9%)	Moderate	High	Low	Yes	Low
Handball	21 (0.2%)	High	Moderate	High	No	High
Ice Hockey	202 (2.0%)	High	Moderate	High	Yes	High
Jumping events (athletics)	343 (3.5%)	Moderate	Moderate	Moderate	No	Moderate
Lacrosse	32 (0.3%)	High	Moderate	High	Yes	High
Marathon (athletics)	203 (2.1%)	Moderate	Low	High	No	Low
Middle/long-distance running (athletics)	614 (6.2%)	High	Moderate	High	No	Low
Modern Pentathlon	83 (0.8%)	High	Moderate	High	No	Moderate
Nordic Combined	39 (0.4%)	Moderate	Low	High	No	Moderate
Polo	67 (0.7%)	Low	Moderate	Low	Yes	Moderate
Race walking (athletics)	100 (1.0%)	Moderate	Low	High	No	Low
Racquet	7 (0.1%)	Moderate	Low	High	No	Moderate
Rowing	657 (6.6%)	High	High	High	No	Low
Rugby	98 (1.0%)	Moderate	Moderate	Moderate	Yes	High
Sailing	455 (4.6%)	Moderate	High	Low	No	Low
Shooting	569 (5.8%)	Low	Low	Low	No	Low
Skeleton	1 (0.0%)	Moderate	High	Low	Yes	Moderate
Soccer	783 (7.9%)	Moderate	Low	High	Yes	High
Speed Skating	72 (0.7%)	High	High	High	Yes	Moderate
Sprint (athletics)	719 (7.3%)	Moderate	Moderate	Moderate	No	Low
Swimming	434 (4.4%)	High	Moderate	High	No	Low
Tennis	245 (2.5%)	Moderate	Low	High	No	Low
Throwing events (athletics)	316 (3.2%)	Moderate	High	Low	No	Low
Weightlifting	133 (1.3%)	Moderate	High	Low	Yes	Moderate
Wrestling	487 (4.9%)	High	High	Moderate	Yes	High

*According to the American College of Cardiology.[26] ** According to the American Academy of Paediatrics.[27]

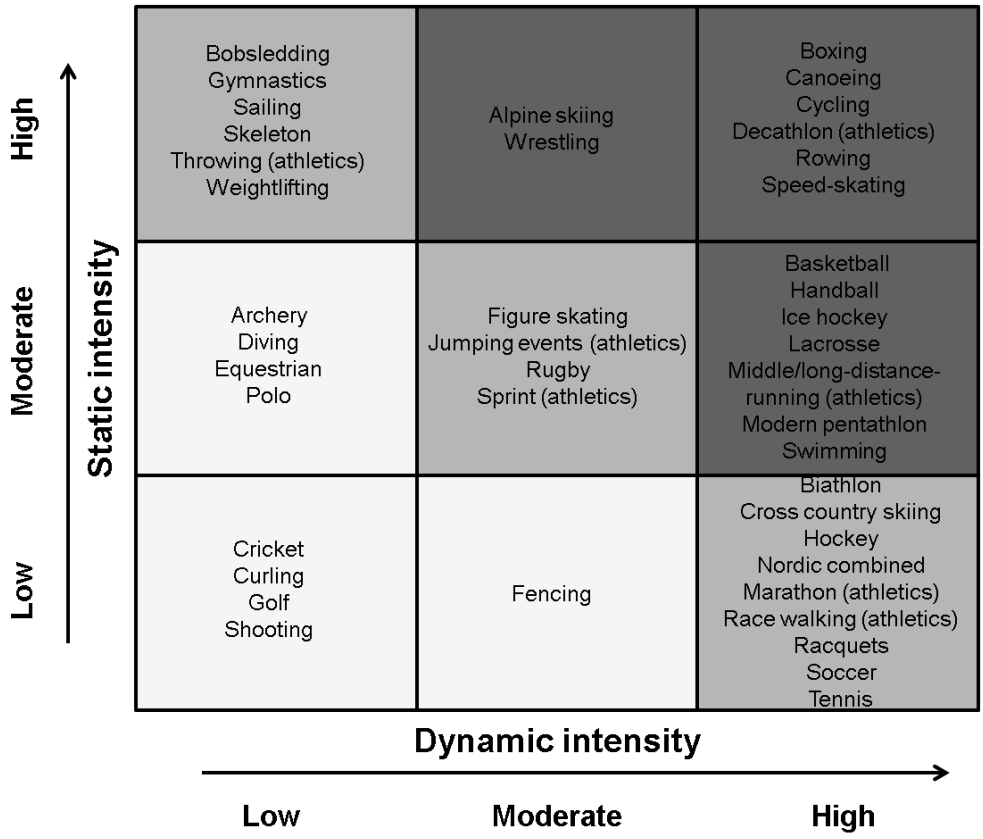

Figure 2. The 43 Olympic disciplines classified in categories of static and dynamic intensity as well as three categories of low, moderate and high cardiovascular intensity (from yellow to red). According to the American College of Cardiology.[26]

We first calculated hazard ratios for mortality dependent on different levels of exercise intensity. Since the participants came from different birth cohorts, we adjusted all our analyses for year of birth, which, as expected, was correlated with mortality. Next, we adjusted for sex and nationality, which were also, correlated with mortality (data not shown). Table 2 shows hazard ratios for mortality for different levels of cardiovascular, static and dynamic intensity in both the univariate and multivariate analysis. Engagement in disciplines with increasing cardiovascular intensity was not associated with a significant higher mortality risk; the hazard ratio for moderate intensity was 1.01 (95% CI: 0.96 to 1.07, p = 0.71) and for high intensity it was 0.98 (95% CI: 0.92 to 1.40, p = 0.46). The multivariate analysis revealed similar results, as shown in table 2. Analysis of

the static and dynamic component separately, showed similar non-significant results. The univariate analysis showed a small beneficial effect of moderate static exercise but this was not reflected in a lower hazard ratio in those engaged in disciplines with high intensity static exercise.

Table 2. Hazard ratios of mortality for athletes in disciplines with different intensities of exercise.

Intensity	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Cardiovascular						
Low	Ref.			Ref.		
Moderate	1.01	0.96-1.07	0.71	1.04	0.95-1.15	0.40
High	0.98	0.92-1.04	0.46	1.05	0.89-1.25	0.58
Static						
Low	Ref.			Ref.		
Moderate	0.94	0.89-0.99	0.02	0.93	0.85-1.01	0.09
High	0.99	0.94-1.04	0.62	0.95	0.85-1.07	0.40
Dynamic						
Low	Ref.			Ref.		
Moderate	0.94	0.89-0.99	0.03	0.94	0.87-1.01	0.09
High	0.97	0.92-1.02	0.19	0.94	0.83-1.06	0.34

Data are expressed as hazard ratios (HR). Univariate analysis adjusted for sex, year of birth, and nationality. Multivariate analysis additionally includes all types of exercise intensity (cardiovascular, static and dynamic intensity) in the model.

We also studied the effect of bodily collision and physical contact on mortality (Table 3). Athletes engaged in disciplines with high risk of bodily collision had 11 percent higher mortality risk when compared to athletes who were not exposed (HR 1.11, 95% CI: 1.06 to 1.15, p<0.001). When comparing athletes who had performed in disciplines with various levels of physical contact it was shown that, those who participated in sports with moderate contact only, did not suffer a higher mortality risk. However, athletes who were exposed to high levels of physical contact had a 16 percent higher mortality risk, when compared to athletes with low physical contact (HR 1.16, 95% CI: 1.11 to 1.22, p<0.001). These higher mortality risks remained similar in the multivariate analysis whereas the hazard ratio for bodily collision became non-significant.

We have additionally performed similar analyses as above in various subgroups: males only, deaths after age 50, born before 1900 and born after 1900. The results are presented in figure 3. In none of the subgroups, exercise at high cardiovascular intensity

was associated with a mortality risk reduction. However, when studying the risk of bodily collision and high physical contact we found a significant higher mortality risk in all these subgroups.

Table 3. Hazard ratios of mortality for athletes in disciplines with different risk of bodily collision and physical contact.

Sport type	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Bodily collision						
No	Ref.			Ref.		
Yes	1.11	1.06-1.15	<0.001	1.03	0.98-1.09	0.25
Physical contact						
Low	Ref.			Ref.		
Moderate	0.97	0.93-1.02	0.25	0.96	0.92-1.01	0.16
High	1.16	1.11-1.22	<0.001	1.13	1.06-1.21	<0.001

Data are expressed as hazard ratios (HR). Univariate analysis adjusted for sex, year of birth, and nationality. Multivariate analysis additionally includes both bodily collision and physical contact in the model.

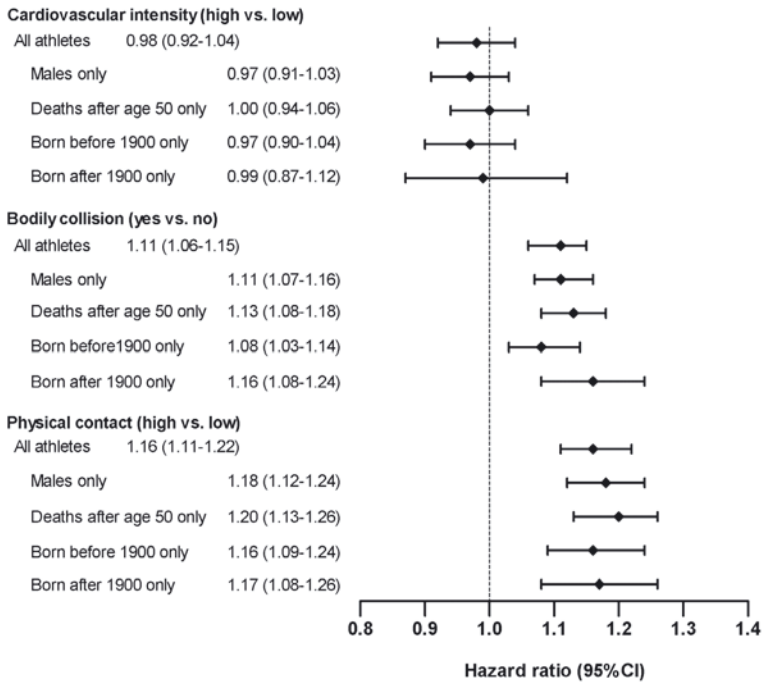

Figure 3. Hazard ratios of mortality (95% confidence intervals) in former Olympic athletes dependent on cardiovascular intensity, bodily collision and physical contact. Analyses adjusted for sex, year of birth and nationality.

DISCUSSION

Our results show that former Olympic athletes who engaged in disciplines with high cardiovascular intensity had similar mortality risks when compared to athletes from disciplines with low cardiovascular intensity. This would indicate that engaging in cycling and rowing (high cardiovascular intensity) had no added survival benefit when compared to playing golf or cricket (low cardiovascular intensity).

Although it is a daunting task to compare nowadays sport activity with that during the first series of the games, the current analysis is sobering for all those athletes that trained so hard to qualify for the London Olympics in 2012. Moreover, our analyses do point to a potential risk for those engaged in disciplines with a high risk of bodily collision and/or high levels of physical contact. As the higher mortality risk persisted when studying death after age 50 this increased risk could not be explained by the death of young athletes due to trauma. We consider it more likely that the higher mortality risk reflects the effect of gradual accumulation of multiple bodily injuries during sport activities. In line, previous studies have shown that bodily collisions and or fierce physical contacts are responsible for a large proportion of the total burden of injuries.[8,28] Next to the direct impact, these injuries may have long lasting detrimental effects and aligns with the generalized theory of ageing. For instance, repetitive head blows, especially in boxers, are associated with cognitive impairment, early onset dementia, and a reduced life expectancy.[29-30]

Our findings stand in contrast to several other studies showing late-life mortality benefit in very well trained athletes.[31-34] A possible explanation could be that these studies only included moderate exercise intensity. Other studies however, described a late-life survival advantage for endurance athletes who had trained at high physical intensity.[22-24,35] But, all previous observations may suffer a bias, as trained athletes differ more from the general population than in physical fitness only. We consider the present comparison of former Olympic athletes who performed their sports at different physical intensity more robust than a comparison between trained athletes and individuals from the population at large. This interpretation is strengthened by the fact that outcomes were congruent in all domains of physical intensity, ie. cardiovascular, static and dynamic intensity.

In this study, we used data from athletes who participated in the Olympic games from 1896 until 1936. Hence, outcomes are considered to reflect late-life consequences of intensive exercise programs that were en vogue 70 to 110 years ago. Since then, training programs, especially on a (semi)professional level, have changed substantially.

Nowadays top-athletes not only train more often and more intense, trainings have also become more individualized and specifically focused. Moreover, medical care to prevent permanent damage is undoubtedly better, and could explain why in the past potential benefits of intensive physical training where overwhelmed by tradeoffs later in life. We do not have access to any data that allows for a valid comparison of use of anabolic steroids and other stimulating substances, but many would argue that the use was probably less prevalent in the past than it is now. For all of these reasons one should be carefull to extrapolate the present findings to the late-life effects of present day training schemes.

Regarding the negative impact of bodily collision and fierce physical contact, it is important to realize that present sporting activities have become far more extreme with regard to velocity, g-force and other mechanical strains. Collisions and physical injuries could therefore have more impact nowadays, despite better protective aids and medical treatment. Our findings could well underestimate the late-life effects of the gradual accumulation of permanent damage due to repeated collisions and injuries that nowadays top-athletes are exposed to.This having said, there are several potential confounders that could decrease or further increase the hazard ratios for mortality that we have found. These include unknown factors such as the total number of years spent in training, age at which intensive training ceased, the intensity of exercise after the athletes withdrew from competitive sports, specific behaviour in specific types of sports, specific personal characteristics depending on the type of sports, etc. Also, it should be noted that beneficial effects of exercise could be counterbalanced by detrimental effects of (acute) cessation of physical exercise resulting in a net neutral effect.

Although we did not find arguments that former Olympic athletes from disciplines with high intensive exercise suffer a higher mortality risk, one should have a moment of caution before engaging in disciplines with risk of bodily collision and or fierce physical contact. This notion may help to explain an historical fact. Before Pheidippides exclaimed νικωμεν (we have won) and collapsed, he had not only ran from Marathon to Athens, but had fought in the battle of Marathon before that. It is tempting to speculate that it was not the run from Marathon to Athens, but the effect of armed force that has led to his tragic death.

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Chapter 9

ARTS AND AGEING; LIFE EXPECTANCY OF HISTORICAL ARTISTS IN THE LOW COUNTRIES

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ABSTRACT

Practicing arts has been linked to lowering stress, anxiety and blood pressure. These mechanisms are all known to affect the ageing process. Therefore, we examine the relation between long-term involvement in arts and life expectancy at age 50 (LE50), in a cohort of 12,159 male acoustic, literary and visual artists, who were born between 1700 and 1899 in the Low Countries. We compared the life expectancy at age 50 of the various artists with the elite and middle class of that time. In the birth cohorts before 1850, acoustic (LE50:14.5-19.5) and literary artists (LE50:17.8-20.8) had a similar life expectancy at age 50 compared to the elite (LE50:18.0-19.0). Only visual artists (LE50:15.5-17.1) had a lower life expectancy at age 50 compared to the elite at that time. For the most recent birth cohorts from 1850 through 1899, the comparison between artists and the elite reversed and acoustic and literary artist had a lower life expectancy at age 50, while visual artists enjoyed a similar life expectancy at age 50. Although artists belonged to the middle socioeconomic class and lived predominantly in urban areas with poor living conditions, they had a life expectancy similar to the elite population. This is in line with observed favourable effects of practicing arts on health in the short-term. From our historical analysis, we hypothesize several mechanisms through which artistic creativity could influence the ageing process and life expectancy. These hypotheses, however, should be formally tested before any definite conclusions on effects of arts on ageing can be drawn.

INTRODUCTION

Since ancient times arts have been used for therapeutic purposes to enhance health. Hippocrates played music for his mental patients and Aristotle described music as a force that purified the emotions [1]. In the thirteenth century, Arab hospitals also contained music-rooms for the benefit of the patients [2]. Since that time, colleges and universities developed programs to train musicians how to use music for therapeutic purposes. Also today, acoustic, literary and visual arts are used to improve the health conditions in chronically ill patients [3-5]. Current research has shown favourable effects of engaging in arts on health, via several mechanisms such as reducing stress, anxiety, pain and blood pressure or improving the immune response and quality of life [6]. Via such mechanisms, artistic interventions can increase general health, decrease doctor visits, and reduce medication use and improve strategies to cope with chronic diseases [3,6].

Many of the above described effects of arts on health, are also known to affect the ageing process. High levels of stress, blood pressure or anxiety, have been found to increase the risk of ageing-related diseases, such as cardiovascular disease [7,8]. In addition, lower stress and anxiety are strongly linked with better well-being, which again is associated with longevity [9-14]. It is therefore of interest to study the long term effects of performing arts on life expectancy. Up to now, this has been only studied on the short term, and the effect of practicing arts on ageing and life expectancy remains unknown. One earlier historical study [15] has shown that visual artists enjoyed a life expectancy that was similar to the life expectancy of the elite, but the question remained whether this was due to their artistic profession or due their socioeconomic status or other determinants. No studies have been performed on the life expectancy of other artists.

Therefore, we studied the relation between long-term involvement in arts and life expectancy at age 50, in a unique historical cohort of 12,159 male artists from different disciplines, who were born between 1700 and 1899. By studying different groups and types of artists we gain more insight in whether the observation that visual artists have a similar life expectancy as the elite is a true 'art-effect' or an 'artefact' of socioeconomic status, selection or other another determinant. This is the first time that the historical life expectancy of different artists is studied in relation to each other and the elite. The aim of this study was to examine ageing-related or senescent mortality, which increases with age more than non-ageing, accident- related mortality, which is also described as background mortality that does not rise with age [16]. A better understanding of the

possible favourable effects of engaging in arts on ageing is of great interest, since it could point to possible public health interventions that not only increase the length but also the quality of life.

MATERIALS & METHODS

Data

We retrieved data from three different databases. Because of the small number of female artists in historical times, we have only studied male artists. Also, because we are interested in ageing-related or senescent mortality and not in child or background mortality, we confined the analysis to people who lived at least till 25 years of age.[16] The Dutch Music Institute (Nederlands Muziek Instituut, The Hague) [17] provided data of 1,543 acoustic artists, comprising both composers (81.7%) and musicians (19.3%). From the total of 1,543 acoustic artists, the sample was reduced by removing the individuals for which the birth year was unknown (125) and additionally those for whom the year of death was unknown (211). Finally, because we place the restriction that the artists should have survived up till age 25, we removed 54 acoustic artist who died before age 26, resulting in a remaining group of 1,153 acoustic artists that we included in our analysis. Next, the Biographic Portal (Biografisch Portaal), a national institute which collects scientific information about leaders and prominent figures from Dutch history, provided a group of 742 literary artists [18]. The group of literary artists consists mainly of poets. From the total of 742 literary artists, the sample was reduced by removing 67 individuals who were born before 1700 and 75 were born after 1899. From the remaining 600 literary artists, we excluded 92 women (we only focus on men). Next, 3 literary artists died before age 26, which resulted in a final sample of 505 literary artists. We derived data of 13,942 visual artists from the RKD-artists database, hosted by the Dutch Institute for Art History (Rijksbureau voor Kunsthistorisch Documentatie, The Hague) [19] This database exists of painters (87,8%) and sculptors (12,2%). For an extensive description of the visual artist data we refer to an earlier study [19]. From the total of 15,419 visual artists Van Poppel et al. [15] used, we removed those who were born before 1700 (3,339) and born after 1899 (1,477) and those who died before age 26 (102). We ended up with a sample of 10,501 visual artists. Finally, we obtained 9,388 elite individuals from the Biographic Portal [18]. This group contained individuals from several occupational fields, including church, education, science, government, nobility and royals, trade and industry, defence forces, judicial system and colonial overseas. The largest subgroup among the elite was from Church, i.e. 2,765 people (31.6%). The majority of all groups consisted of men (78.4-96.4%). From the total of 9,388 elite individuals, we excluded 2,697 who were

born before 1700 and 579 who were born after 1899. From the remaining 6,112 elite, we excluded 167 women. From the residual 5,945, 20 died before age 26 and we finally included 5,925 in our analysis.

Historical data on individuals from the middle class were only available for the most recent birth cohorts from 1850-1899. We use data that relate to the country as a whole, thus we can take into account the situation of people living in a variety of ecological, social, and economic circumstances, covering the countryside and small and big towns. For this study we have used data collected in the framework of the Historical Sample of the Netherlands (HSN). From the total of 3,996 individuals in that sample, 1,101 were classified as being middle class. Of these individuals 24 died before age 26 and hence we included 1,077 people in our analysis. For a detailed description of these data and how the socioeconomic status was assessed we refer to an earlier publication by Schenk & van Poppel [20].

All databases are available on request. The birth cohorts covered by these databases lived from the 18th century until the end of the 1900s. Every individual is only once assigned to a group in the database. Hence, there is no overlap between the groups. It is possible that some elite people also practiced arts occasionally, but if such an elite person practiced arts more professionally, he would have been in the artist-database.

By studying the life expectancy at age 50, we have tried to reduce the effect of background mortality, such as early deaths due to child disease, and at middle age and other non-ageing related diseases. Additionally, by studying life expectancy at age 50, we overcome a survivor treatment selection bias , also known as 'immortal time bias'. In the case of artists for instance, they have to survive up to a certain age in order to become successful and famous artist. A recent example from the literature is a study that suggested a survival advantage for Oscar winners, which appeared to be attributable to 'immortal time bias' [21,22].

Statistical analysis

We carried out separate analyses by four different birth cohort groups: people born between 1700 to 1749, born between 1750 to 1799, born between 1800 to 1849, and born between 1800 to 1899. The data were analyzed using Gompertz hazard models for each discipline and cohort separately. Based on the estimated model we calculated the implied life-expectancy. For the visual artists we sometimes knew only an interval, sometimes 10 years wide, in which they were born and/or died. We used a previously published method to account for this interval censoring [23].

In analyses of human mortality a Gompertz distribution [23] is known to fit well [24-26]. This distribution has two parameters, a shape α and a scale parameter β. The hazard rate, the force of mortality, at age *t* increases exponentially over the life span, $\lambda(t) = e^{\alpha t+\beta}$. The density, *f*, and the survival, *S*, for a duration *t*, in a Gompertz distribution are:

$$f(t) = e^{\alpha t+\beta}\exp\left(-\frac{1}{\alpha}e^{\beta}\left(e^{\alpha t}-1\right)\right),\ S(t) = \exp\left(-\frac{1}{\alpha}e^{\beta}\left(e^{\alpha t}-1\right)\right)$$

Based on the observed years of birth and death we calculated the implied age of death. For the visual artists we sometimes knew only an interval, sometimes 10 years wide, in which they were born and/or died. In those situations a *minimum* length of life and a *maximum* length of life could be derived. When the date of birth was known exactly but the death was only recorded as occurring within a given interval the *minimum* length of life was calculated as the difference between the date of birth and the earliest date of death reported, and the *maximum* length of life as the difference between the date of birth and the latest date of death. When the date of death was known exactly but the date of birth was recorded as occurring within a specific time-interval, the *minimum* length of life was calculated as the period from the last possible date of birth until the date of death and the *maximum* length of life as the period from the earliest possible date of birth until the date of death. Finally, when both the date of birth and the date of death were known only approximately and both were recorded as falling within particular time intervals. In such cases, the *minimum* length of life was calculated as the period from the latest date of birth until the earliest date of death, and the *maximum* length from the earliest date of birth until the latest date of death. In Van Poppel et al. [15] the procedure to account for this type of interval censoring are discussed in detail.

In addition, by making it a condition that an individual must have already survived to the age of 25, it is possible to take into account the fact that, to be recognised as an artist, an individual needs to have lived long enough to have produced a notable piece of art.

To estimate the parameters of the model we maximized the joint likelihood, which is the product of the individual likelihood contributions. The individual likelihood contribution is the density for those artists whose exact date of birth and date of death were known. For the visual artists we accounted for the interval censoring described above, see [19] or the appendix. Based on the estimated parameters the life expectancy, LE_{50}, at age 50 can be approximated very well [26].

$$LE_{50} = -\exp\left(\frac{1}{\alpha}e^{\beta+50\alpha}\right)\left(\beta-\ln(\alpha)+50\alpha+\gamma\right)/\alpha$$

where γ ≈ 0.57722 is the Euler-Mascheroni constant. The variance of the life expectancy

at age 50 can be approximated using the delta-method, the standard method in econometrics to obtain the distribution of a nonlinear combination of parameters [27]. Using the estimated LE_{50}'s and their variance we calculated, for each cohort period and for each of the three artist-groups, the difference of the artist life expectancy with the life expectancy of the elite group (assuming independence the variance of the difference is the sum of the variances). The p-values of these tests are reported in Table 2.

RESULTS

We included 12,159 male artists from three different disciplines who were born between 1700 and 1899. The numbers are summarized in table 1. In total 1,153 acoustic, 505 literary and 10,501 visual artists were included. The elite group consisted of 5,925 individuals, born in the same time period. The majority of the individuals (32-69%) were born between 1850 and 1899. Historical data on people from the middle class were only available for the most recent birth cohorts, born after 1850. In total we studied 1,077 individuals from the middle class of that time.

Table 1. Characteristics of study population.

	Acoustic artists	Literary artists	Visual artists	Elite	Middle class
Total n(%)	1,153 (100)	505 (100)	10,501 (100)	5,925 (100)	1,077 (100)
Year of birth n(%)					
1700-1749	38 (3)	17 (3)	681 (6)	940 (16)	
1750-1799	72 (6)	45 (9)	1,303 (12)	1,424 (24)	
1800-1849	243 (21)	130 (26)	2,797 (27)	1,676 (28)	
1850-1899	800 (69)	313 (62)	5,720 (54)	1,885 (32)	1,077 (100)

We analysed the life expectancy at age 50 from the various groups of artist and first compared their life expectancy to that of the elite. Figure 1 shows the life expectancy at age 50 for the birth cohorts from 1700 to 1749, 1750 to 1799, 1800 to 1849 and 1850 to 1899. From 1700 to 1899, there has been an increase in life expectancy in all groups. For the middle class, data were only available for the most recent studied cohorts, in the figure this point estimate is shown as a *star*.

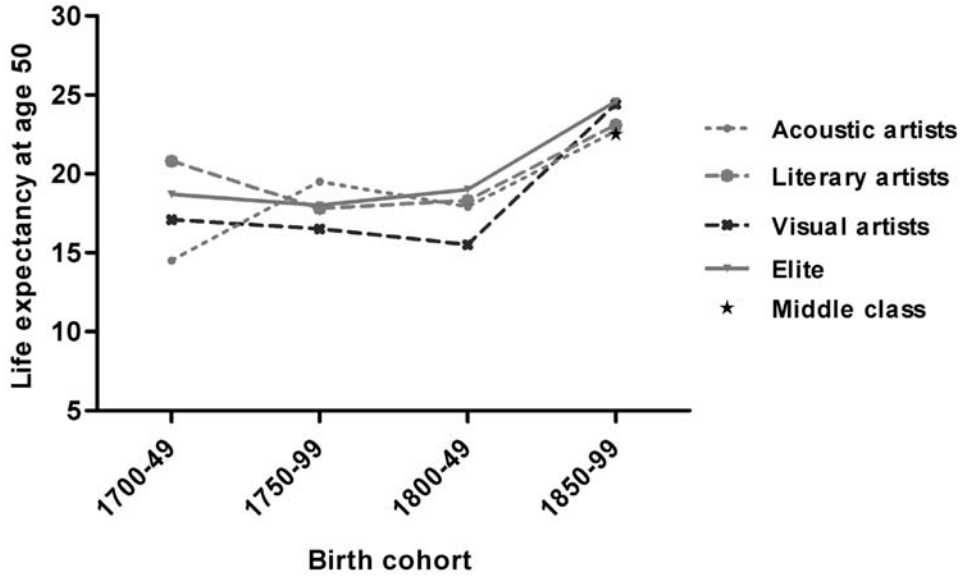

Figure 1. Life expectancy at age 50 of male artists (acoustic, literary and visual), the elite born between 1700 and 1899 and the middle class born between 1850-1899.

Next, we tested whether the life expectancy of the artists was different from that of the elite. Table 2 shows the life expectancies at age 50 of artists and elite, the standard errors and tests of significance. Before 1850 artists had a similar life expectancy at age 50 when compared to the elite of that time, except for the visual artists, who had a significant lower life expectancy at age 50. In the most recent period from 1850 to 1899, this pattern reversed and acoustic and literary artists had a significant lower life expectancy at age 50 than the elite. Visual artists and the elite had a similar life expectancy at age 50 of almost 25 years after 1850. Only for the latest period, data of a middle class population were available. During that period, the middle class had an average life expectancy at age 50 of 22.6 years. The various artists had a higher life expectancy than the middle class at that time, although this reached only significance in the largest group of visual artists.

Table 2. Life expectancy at age 50 (LE50) of artists compared to the life expectancy at age 50 of the elite, who were born between 1700-1899 and to the life expectancy at age 50 of the middle class who were born between 1850-1899.

Year of birth	Acoustic artists		Literary artists		Visual artists		Elite		Middle class	
	LE50 (SE)	P	LE50 (SE)	P	LE50 (SE)	P	LE50 (SE)	P	LE50 (SE)	P
1700-1749	14.5 (2.9)	0.07	20.8 (2.1)	0.17	17.1 (0.6)	0.02	18.7 (0.5)	ref.		
1750-1799	19.5 (1.4)	0.16	17.8 (2.1)	0.46	16.5 (0.5)	<0.05	18.0 (0.4)	ref.		
1800-1849	17.9 (1.0)	0.14	18.3 (1.4)	0.31	15.5 (0.4)	<0.001	19.0 (0.3)	ref.		
1850-1899	22.7 (0.6)	<0.05	23.1 (0.7)	0.02	24.4 (0.2)	0.23	24.6 (0.3)	ref.		
1850-1899	22.7 (0.6)	0.43	23.1 (0.7)	0.26	24.4 (0.2)	<0.001	24.6 (0.3)	<0.001	22.6 (0.4)	ref.

DISCUSSION

Between 1700 and 1849 acoustic and literary artists had a similar life expectancy at age 50, when compared to the elite population of the Low Countries. Only visual artists had a lower life expectancy at age 50 in these birth cohorts. This is striking, since artists belonged predominantly to the middle socioeconomic class [15, 28]. In cohorts born after 1849 acoustic and literary artists had a lower life expectancy compared to the elite, while visual artists enjoyed a similar life expectancy when compared to the elite. Unfortunately, historical data on the middle class population has not been documented. Only for the most recent birth cohorts we have found data, which showed that artists lived longer than the middle class, but this reached only significance in the largest group of visual artists.

Our study differs from a previous study, in which artists were found to have a lower survival compared to popes [29]. Others have shown that visual artists had a relatively high life expectancy, when compared to the elite of their time, which is in line with our observations [15]. We studied different groups and types of artists and found that not only visual, but also, other artists had a similar life expectancy as the elite. Although there are differences between the group sizes of the various artist types, this is the first time that the historical life expectancy of different artists is studied in relation to each other and the elite population. However, whether the observed differences are related to the practicing of art or due to socioeconomic status, selection effects or other characteristics of artists remains to be further studied.

During the studied period from 1700 to 1899, life expectancy increased for both artists and the elite. Possible mechanisms that have driven this increase in life expectancy could be improvements in living conditions, better hygiene and public health [30]. From 1850 onwards, with the epidemiologic transition, the increase in life expectancy is known to be especially driven by improvements in wealth and public health [30]. Up to 1850, visual artists were the only artists having a lower life expectancy than the elite in our study. Earlier it has been shown that painters have a lower life expectancy than sculptors, which was attributed among other factors to differences in exposure to toxic materials [15, 31]. This could partly explain the observed lower life expectancy of visual artists in our study, since the visual artist group consisted primarily of painters (81.7%). Additionally, it is possible that other factors, such as differences in terms of educational level, socioeconomic status or familial background could be behind the difference in life expectancy between visual artists and other artists groups.

It is tempting to hypothesize about possible mechanisms behind our findings. Socioeconomic status is strongly linked to life expectancy [32]. Even today, rich people outlive poor people by seven years in the Netherlands [33]. How socioeconomic status was related to life expectancy in the past is however debated [34]. Historical data suggest that socioeconomic status was not linked to life expectancy as today [35]. By contrast, contemporary data from a rural population in Ghana, have shown that even under those adverse conditions, individuals with a higher socioeconomic status have a considerable survival advantage [36]. In our dataset, there is no information on the socioeconomic status of the individual artists. Little is known in general about the socioeconomic status of artists in historical times, but prior to the industrialization artists usually descended from middle class families [15,28]. Detailed studies on the socio-economic position of visual artists in the first half of the nineteenth century in the cities of Dordrecht and The Hague, have confirmed that the majority of the artists were able to live a rather comfortable life; the most successful were able to earn an income that was higher than that of the middle classes (artisans, merchants, public servants) they originated from [37]. This picture is confirmed by the outcome of a study on the socio-economic position of the visual artists in the second half of the same century in The Hague and Amsterdam. It would seem that in this period the visual artists were quite successful in climbing the social ladder [38]. In the 18th century, the income of musicians was not sufficient to make a living. Some musicians therefore, additionally worked in other professions too; in our study 34% of the acoustic artists were having another profession next to their artistic career. Literary artists also belonged to the middle class in economical terms. Only from the end of the 19th century onwards, by industrialization of book printing techniques, their socioeconomic status improved [39].

The low life expectancy among the middle and lower class has been related to poor sanitation, malnutrition, overcrowding, polluted water, less access to health care and living in unsafe and unhealthy conditions [40]. It is important in this respect that most artists lived in urban areas where their audience and clients lived. Here, poor sanitary conditions and epidemics of infectious diseases used to cause high mortality [15]. This makes it especially striking that the life expectancy of most artists was similar compared to the higher classes with much better living circumstances. After the industrialization, the mass production of cheaper products led to an increased access to musical instruments for people of lower classes. Additionally, living conditions in the cities deteriorated and these processes could have contributed to the lower life expectancy of artists compared to the elite born in the period after 1850 until 1900 [41].

Others have studied several mechanisms through which artistic creativity could have an effect on health and ageing [42-55]. Some have found that art and music interventions can enhance bodily control or improve pain management [43]. In addition, it reduces stress and anxiety with consequent effects upon heart rate, respiration, blood pressure, brain function and immune response [44]. Singing for instance, has been found to increase certain chemicals, such as endorphins (natural pain killers) and immunoglobulin A (immune function), which enhances the pulmonary work out, oxygen intake and increases circulation [45]. Moreover, music distracts one from feelings of illness, gives patients sense of control and lowers their blood pressure [43-45]. Also, music has been found to boost the immune function [46], increase cognitive function [47] and improve memory performance [48], concentration and attention [48]. Music increases physical performance by increasing psychological arousal, reduces feelings of fatigue and improves motor coordination [49, 50]. Studies on visual arts revealed similar results, such as reducing anxiety, improving vital signs, diminished cortisol levels related to stress and improved sleeping patterns [51, 52]. In addition, creative writing such as poetry has been found to have beneficial psychological effects on coping mechanisms for depression and increases the likelihood that patients can stop their antidepressants [53]. Finally, it can boost the immune system and improve pain control [54, 55].

We analysed a unique cohort with artists from three different disciplines over a long time span from 1700 till the end of the next century. The Low Countries form an interesting case to study the effect of arts because of their rich tradition in artistic creativity [15]. A limitation of our study is that the historical records contained very few women and hence, we have only studied the life expectancy in men. Furthermore, it is possible that our database contains only the artists who survived long enough to have the opportunity

to become well known and for that reason also well documented. In this case our observations would be partly explained by survivor treatment selection bias. However, we have tried to overcome this problem by studying life expectancy at age 50.

All in all, we have found that in cohorts born before 1850, acoustic and literary artists had comparable life expectancy as elite groups, despite belonging to middle socioeconomic class and living in urban areas with poor living conditions. Only visual artists had a lower life expectancy compared to the elite. From our historical analysis, we hypothesize several mechanisms through which artistic creativity could influence ageing and life expectancy. These hypotheses, however, should be formally tested before any definite conclusions about the effects of arts on ageing can be drawn.

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Chapter 10

GENERAL DISCUSSION

GENERAL DISCUSSION

In this thesis, we studied the compression and plasticity of old-age mortality during the epidemiologic transition. We focussed on the Netherlands, Japan and Ghana, three countries that have all experienced a different epidemiologic transition. The Netherlands has experienced a classical epidemiologic transition, in which all stages were sequential. Japan is the best known example of an accelerated classic epidemiologic transition, which only took about fifty years. Ghana is currently experiencing a protracted epidemiologic transition, in which the different stages overlap. There are several conclusions we can draw from our studies on old-age mortality trends in these epidemiologic transitions.

MAIN FINDINGS

The first two chapters describe mortality patterns in rural Ghana followed up for a period of nine years. In **Chapter two** we examined the role of socioeconomic status and water source on mortality and fertility decline during the epidemiologic transition. We found that both mortality and fertility declined, accompanied by a shift in the causes of death, which changed from primarily infectious causes to non-infectious. However, both the decline in mortality and fertility were found to be similar in the poor and rich groups as well as in the groups which have access to (un)safe water source. Hence there must be other determinants that drive the epidemiologic transition in this rural area in Ghana. These findings are in line with the current theories on determinants that drive the protracted transition in rural African countries. Some have shown that public health interventions, such as immunization or maternal and child health programs are the main drivers behind the protracted epidemiologic transition.

In the following **chapter three** we studied the seasonal variation in mortality in rural Ghana. We found that mortality due to infectious diseases occurred mainly in September during the wet season, while mortality due to non-infectious causes occurred mostly in April during the dry season. This indicates that during the epidemiologic transition mortality not only shifts from child to old-age mortality, and from infectious to non-infectious causes of death, but that the distribution of deaths over the seasons probably changes as well. This is important for future public health interventions in rural Africa.

Next to changes in seasonal variation in mortality during the epidemiologic transition, we studied the process of the compression of mortality during the epidemiologic transition in Japan and the Netherlands in **chapter 4**. Our observations show a continuing shift of

mortality to higher ages, together with a compression of the age-at-death distribution that appears to have reached a limit, in both Japan and the Netherlands. The observed limit to the compression of mortality is in line with the current theory on ageing, as a stochastic accumulation of damage over time. Due to the stochastic element in the ageing process, there will always be variation in the rate of ageing and hence, the limit to the compression of mortality has to be above zero. Accordingly, we have observed that the limit of mortality compression is reached at an age-band of 12 years in which fifty percent of the annual mortality occurs. This indicates that differences in lifespan within a homogeneous population can never become less than the age-band when mortality compression has reached a limit. Ultimately this limit is determined by the random variation in the pace of ageing.

In addition to the compression of mortality, we examined the compression of morbidity in **chapter five**. Now that life expectancy is continuously on the rise, it is questioned whether the extra years are lived in good or in ill health. Analysis of the trajectories in healthy life expectancy revealed that during the epidemiologic transition, there has been an expansion of morbidity in the Netherlands. Hence, individuals live with chronic diseases for more years, which could reflect both early diagnosis and changed lifestyles. By contrast, we observed a compression of disability in both women and men, as life expectancy without disabilities increased parallel to the increase in life expectancy. Overall, by screening for chronic diseases and proper treatment of for instance hypertension, we postpone or even prevent disability, including in this case cardiovascular disease, and increase life expectancy. We did observe sex differences in life expectancy which persisted up to old age. At the highest ages however, men and women can expect a similar number of years of healthy life expectancy. At the end of life there remains a period of disability that can be postponed, but not further compressed. Hence, the need for care will be remain to be concentrated at the end of life. In **chapter six** we discuss the societal implications of this and argue that it is time for people to realise that they can foresee a healthier and longer life and that they have to plan their life course accordingly.

In **Chapter seven** we study the plasticity of mortality at old age in a natural experiment in Japan. In general, studying factors that impact directly on old-age mortality is challenging. In most countries, improvements in the environment and living conditions that have occurred during the epidemiologic transition, has changed relatively smoothly over time. The case of Japan is exceptional because of the relatively adverse living conditions for the general population during the first half of the 20th century, after which an accelerated transition resulted in rapid improvements after 1950. Studying different birth cohorts in

Japan, that were exposed to different extents to the rapid improvements, we have shown that environmental improvements in late life can reduce old-age mortality independent of exposures in early life. This result indicates that mortality remains highly plastic up to old age. Modern preventive strategies however, are mostly focused on the young. Our observations from Japan strengthen the notion that preventive measures later in life can also have great potential benefit.

In **chapter eight**, we have studied whether or not high intensity physical exercise has a health benefit over low intensity exercise in a cohort of former Olympic athletes. Here we show that athletes from disciplines with high intensive exercise have a similar mortality risk when compared to athletes from disciplines with low intensity exercise. Rowing for instance, has no added benefit to reduce mortality risk when compared to playing golf. However, one should have a moment of caution before engaging in disciplines with risk of bodily collision and or physical contact, since athletes from such disciplines suffered an increased mortality risk, which persisted up to old age.

Finally, in **chapter nine,** we studied the life expectancy of historical artists compared to the elite in the Low Countries. These data revealed that although artists belonged to the middle socioeconomic class, they had a similar life expectancy when compared to the elite of that time. We hypothesize several mechanisms through which artistic creativity could influence life expectancy. However, these hypotheses should be formally tested before any definite conclusions on effects of the arts on life expectancy can be drawn.

Overall, when countries shift from a pre- to a post-transitional stage, mortality decreases and an increasing number of people live up to old age. In addition, mortality is compressed to a narrower age interval in which most of the annual deaths occur. This compression of mortality reaches a limit as soon as countries enter the post-transitional era. Furthermore, during the last stage of the epidemiologic transition, with the appearance of 'diseases of affluence', we have observed an expansion of morbidity and more years are lived with chronic diseases. By contrast however, life expectancy without disability is increasing parallel to the increase in life expectancy indicating a compression of disability. Due to earlier diagnosis more years are lived with chronic diseases, but this allows for early treatment that in the end postpones or even prevents disability. In general, mortality remains highly plastic up to old age, as indicated by the continuous rise of life expectancy and the shift of the age-at-death distribution towards higher ages.

Strengths and weaknesses

Studies on the plasticity and compression of old-age mortality have been primarily demographic and descriptive in nature, presenting time trends only.[1-6] In this thesis we not only studied time trends, but also linked mortality changes to life expectancy. Additionally, we have studied the trends in old-age mortality in the theoretical framework of the biology of ageing and we have tried to get further insight in the underlying mechanisms of both the plasticity and compression of mortality.

There are also limitations of the studies in this thesis. In general, causal relationships between determinants and outcomes are best studied using an experimental study design with a specific intervention.[7] We have tried to get a better understanding of specific determinants and the underlying process of mortality changes, based on experiments of nature. Hence, it is hard to draw any definite conclusion about causal relationships between the various determinants of old-age mortality. Experiments from nature do allow us to test some pseudo-interventions that are not possible in normal experiments. Another limitation is that we have studied the mortality patterns in three countries only. However, the Netherlands, Japan and Ghana are unique cases, providing an example of different epidemiologic transitions.

IMPLICATIONS FOR SOCIETY

The plasticity of mortality as we have observed during the epidemiologic transition has resulted in a rising number of people that have the privilege to live up to old age while maintaining good health. However, this trend can only continue when we adapt our society to accommodate our growing elderly population. This comes with several societal challenges in terms changes in formal and informal care, health care costs and pension policies. Some of the implications will be discussed below.

Dependency ratio

The epidemiologic transition has led to both low fertility and low mortality, which has resulted in ageing populations, especially in today's western societies.[8-10] The age composition in these populations has changed from predominantly young individuals towards an age composition in which the proportion of children, adults and elderly is almost equal.[10,11] This is one of the most common starting points for policy makers and is often measured as the dependency ratio [12-16]. This ratio is an age-based indicator for the burden on the productive labour population and is given as the ratio of non-productive per productive individual. Based on the observations in our studies,

however, we have several remarks concerning the dependency ratio as a measure for policy makers. First, while the old-age dependency ratio is increasing, one should not overlook that the total dependency ratio is influenced by the youth dependency ratio as well. The latter ratio (0-19 years divided by 20-64 years) has decreased during the last 50 years and will further decline in the future. The old-age dependency ratio (65+ divided by 20-64 years) has increased and is expected to do so in the coming decades. The total dependency ratio however, has not increased, and has in fact slightly decreased.[10,11] A second reason dependency ratios are inaccurate is because it categorizes all people aged 65 years or older as dependent. As it is an indicator based solely on chronological age, it overlooks that not all individuals above age 65 are dependent. Especially as we have shown that with the shift of mortality to higher ages, life expectancy in good health and without disabilities also increases. Policy makers should take this into account when using the total dependency ratio as a starting point for future policies of formal and informal care, health care costs and pension systems.

Health care costs

The average level of long-term care expenditure has been shown to rise with age [13]. It is questionable however, whether an ageing population is the major driver of the ever increasing health care expenditure. For example, it has been shown that health care costs are concentrated in the last years of life.[17,18] This is in line with our findings of a fixed period of disability at the end of life that cannot be further compressed. This implies that irrespective of how old one gets, the disability burden and the highest health care costs will be in the last year of life. In addition, the demand for health care will be postponed to higher ages. All in all, although higher ages are known to be associated with higher long-term care expenditure, it is not the main explanation for the rise in health care costs. Alternatively, there has been an expansion in the use of medical technology during the last decades. These technical innovations have fostered the rise in health care expenditure and hence have played a major role in the overall increase of health care costs.[19,20]

Pension policies

We have shown that human lifespan is continuously on the rise. This plasticity not only results in longer lives for individuals, but also for more people reaching old age. This has several consequences for many countries that offer their older citizens financial security through pension systems. In a social pension system, financial resources are redistributed from the working population to the retired population.[10] In other words, as the old-age dependency ratio increases, a smaller working population is responsible for a relatively larger retired population. This will become a major burden for pension

systems. Although life expectancy and healthy life expectancy are still increasing, many countries still have a relatively early withdrawal from the labour market, at an average age below 60.[11-13] Increasing pension age not only helps to reduce the burden for pension systems, but it also results in a larger labour force.[13] Most countries however, are hesitant to take the necessary measures in order to achieve this.[14] It is now time to act and make sustainable policies that meet the needs from ageing societies.

IMPLICATIONS FOR MEDICINE

Next to the societal implications of the plasticity of old-age mortality, there are also some specific implications for medicine. Below we will briefly discuss the implications in terms of 'evidence-based medicine', 'evidence-based prevention', health care structure and medical education.

Evidence-based medicine

Now that in most countries more and more people reach old age, we should rethink 'evidence-based medicine'. Currently the evidence is still based on studies in middle aged adults, with a single disease. This is problematic in two ways. First, most elderly have multiple diseases at the same time, which brings new challenges.[24] There are little to no randomized clinical trials including elderly with multimorbidity.[25] Second, ageing comes with some physiological changes that change the pharmacokinetics and pharmacodynamics.[26] Consequently, known effective treatments at middle age might lead to different health outcomes at old age. Hence, future research should focus on clinical trials with elderly having multimorbidity in order to get evidence-based medicine for this group and address the current needs of our society. Although our studies indicated a continuous rise in life expectancy and healthy life expectancy, this can only continue to increase if we adapt our medicine to fit the new older patient population. It is important to mention here that the primary aim should be to improve quality of life and that only as a result life expectancy will increase.

Evidence-based prevention

We have observed that mortality remains highly plastic up to old age. This indicates that in addition to life-course approaches to improving health and well-being, preventive measures at older ages can deliver great benefits. Apart from physical exercise, evidence for effective preventive measures is poor, especially when it comes to prevention at old age.[27] Since most age-related diseases are highly determined by life-style, development of 'evidence-based prevention' for elderly should be primary objective for ageing societies

The observed plasticity of ageing should be encouraging to study specific preventive measures. This urgently needs to be placed on the research agenda[27].

Health care structure

With the increase in life expectancy, there has been an expansion of chronic diseases, which increases the need for long-term care. In addition, there has been an increase in the prevalence of multimorbidity, which is becoming the norm rather than the exception. Nowadays, health care structure is insufficient and not adapted to the current older patient population. Current health care is mainly focussed on acute problems and short-term solutions. Chronic diseases demand for long-term care with active involvement of patients themselves. In the current system, patients with multiple chronic diseases do not receive optimal care. It has been shown that enhancing self-management of chronically ill patients not only leads to patients being in control of their own health, but it also improves health care outcomes.[28] In addition, formal care should shift towards a multidisciplinary approach, where different specialists work together as a team. Multimorbidty requires a patient-centred approach with a multidisciplinary team that provides holistic care. Overall, we have to rearrange our health care structure in a way that patients become actively involved as being their own health manager and formal care is patient-centred with a holistic approach.

Medical Education

Due to the plasticity of mortality, the proportion of elderly patients has increased rapidly during the last decades. Since this trend is expected to continue, future medical doctors should be prepared for a patient population containing predominately elderly. However, medical education on the treatment of elderly patients is currently unsatisfactory.[29] Both medical students and current medical specialists are trained to treat patients with single diseases and hence, are not prepared for the largest group of their patient population. In order to improve medical care for the elderly, it is essential that all health care professionals receive a basic training about the complex care for elderly in terms of multimorbidity, as well as in how to deal with the physiological changes that come with age.

Final conclusion

Overall, our studies show the plasticity of old-age mortality. There is no indication that we have reached the limits of this plasticity, which is an encouraging finding. Hence, we can be optimistic about the future, but we also have to adapt to the new reality that people live longer and more years are lived in good health.

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NEDERLANDSE SAMENVATTING

DE COMPRESSIE EN PLASTICITEIT VAN STERFTE OP HOGE LEEFTIJD

INTRODUCTIE

Gedurende de laatste eeuw is de levensverwachting bij geboorte wereldwijd gestegen.[1] Tot op heden is er nog geen limiet en zet deze trend zich voort.[2] Dit roept veel vragen op over hoe de toekomst eruit zal zien. Nemen binnen een land de verschillen in levensverwachting toe of af? Betekent langer leven ook langer gezond leven? Kunnen we sterfte op hoge leeftijd nog verder terugdringen? In dit proefschrift proberen we antwoorden te vinden op dergelijke vragen, door de mechanismen die de drijfveer zijn achter de continue sterftedaling beter te begrijpen. In het bijzonder bestuderen we de compressie en plasticiteit van sterfte op hoge leeftijd die hebben plaatsgevonden gedurende de epidemiologische transitie. Hieronder volgt een korte introductie over zowel de epidemiologische transitie als de compressie en plasticiteit van sterfte.

De theorie over de verschillende stadia van de epidemiologische transitie is voor het eerst beschreven door Omran in 1971.[3] Tijdens deze transitie is er een sterfte daling, gevolgd door een daling in vruchtbaarheid. Daarnaast is er een verschuiving in de samenstelling van doodsoorzaken van infectieus naar meer niet-infectieuze doodsoorzaken veroorzaakt door chronische ziekten. De veranderingen in sterfte en vruchtbaarheid tijdens de epidemiologische transitie kunnen op verschillende manieren verlopen door de tijd. In het klassieke model van de transitie zoals deze is verlopen in de huidige post transitionele landen, verlopen de verschillende stadia van de epidemiologische transitie sequentieel. Daarnaast heeft in sommige landen de epidemiologische transitie versneld plaatsgevonden ten opzichte van het klassieke model. Japan is hiervan het meest bekende voorbeeld, waar de gehele transitie heeft plaats gevonden in minder dan vijftig jaar.[4] In huidige ontwikkelingslanden in transitie vindt er juist een vertraagde epidemiologische transitie plaats, waarin ook verschillende stadia met elkaar overlappen.[3]

Gedurende de epidemiologische transitie neemt de levensverwachting toe en groeit het aantal mensen dat een hoge leeftijd bereikt. Dit gaat gepaard met een afname in de spreiding rondom de leeftijd waarop de meeste sterfte plaats vindt in een bepaald jaar. Dit wordt de compressie van sterfte genoemd.[5] Maximale compressie van sterfte zou betekenen dat alle jaarlijkse sterfte op dezelfde leeftijd plaats vindt. Daar tegenover staat minimale compressie, wat inhoudt dat de kans om te overlijden in een bepaald jaar voor alle leeftijden gelijk is.[6] Gedurende de afgelopen eeuw is er sprake geweest van compressie, maar onduidelijk is hoever deze compressie zich doorzet.[7-9] Naast de compressie van sterfte is er ook de compressie van ziekte. Dit gaat over de vraag of met het stijgen van de levensverwachting er jaren in goede of slechte gezondheid bij komen.

[10,11] Tot op heden is er geen consensus bereikt over het verloop van de compressie van ziekte en sterfte.

Als laatste belichten we de plasticiteit van sterfte op hoge leeftijd. Het is reeds bekend dat een vroege leefomgeving van belang is voor het risico op ziekten later in het leven.[12] Slechte voeding of hoge blootstelling aan infectieziekten vroeg is het leven, zijn geassocieerd met hogere sterfte kansen op latere leeftijd.[13,14] Er is echter geen overeenstemming over het effect van de omgeving op hoge leeftijd.[15-18] Veel studies beschrijven dat het verbeteren van de omgeving op hoge leeftijd geen gezondheidswinst meer oplevert.[16,17] Dat staat haaks tegenover anderen die laten zien dat sterfte ook op hoge leeftijd nog verder te reduceren is.[18] In hoeverre sterfte nog beïnvloedbaar is op hoog leeftijd, is van groot belang in het kader van preventie.[19]

Het doel van dit proefschrift is dan ook om meer inzicht te krijgen in het intrinsieke proces van compressie en de plasticiteit van sterfte op hoge leeftijd gedurende de epidemiologische transitie. We doen dit door de sterfte te bestuderen in Ghana, Nederland en Japan, drie landen die de epidemiologische transitie verschillend hebben doorlopen.

OVERZICHT VAN DIT PROEFSCHRIFT

Hoofdstuk één is een algemene introductie van dit proefschrift waarin de theorie over de epidemiologische transitie en de begrippen compressie en plasticiteit van sterfte op hoge leeftijd worden geïntroduceerd. In de volgende hoofdstukken bestuderen we de epidemiologische transitie in Ghana. Om te beginnen met **hoofdstuk twee**, waarin we de rol van sociaal economische status en drink water hebben bestudeerd op de afname van sterfte en vruchtbaarheid gedurende de epidemiologische transitie. Deze twee factoren hebben een belangrijke rol gespeeld bij de afname in sterfte en vruchtbaarheid tijdens de traditionele epidemiologische transitie in westerse landen. Onze observaties in Ghana laten zien dat er een epidemiologische transitie gaande is in het onderzoeksgebied. Zowel sterfte als vruchtbaarheid zijn sterk gedaald gedurende de follow-up periode van 2002 tot 2011. Daarnaast heeft er een verschuiving plaats gevonden in de samenstelling van doodsoorzaken, die werden eerst gedomineerd door infectieziekten, maar nu door niet-infectieuze oorzaken. In tegenstelling tot de traditionele transitie in westerse landen, was er geen verschil in afname van sterfte of vruchtbaarheid tussen mensen met een hoge versus lage sociaaleconomische status en ook niet tussen de groepen met toegang tot veilig of onveilig drinkwater. Er zijn dus andere factoren die de 'vertraagde' epidemiologische transitie drijven in Ghana.

In **hoofdstuk drie** hebben we de variatie van sterfte over de seizoenen bestudeerd in Ghana. De grootste piek in sterfte door infectieuze oorzaken was in september gedurende het regenseizoen, terwijl de grootste piek met sterfte door chronische aandoeningen te zien was in April, gedurende het droge seizoen. Deze bevindingen laten zien dat gedurende de epidemiologische transitie, de sterfte niet alleen verschuift van jong naar oud en van infectieuze naar meer chronische doodsoorzaken, maar dat de verdeling van sterfte over de seizoenen mogelijk ook verschuift.

Naast de epidemiologische transitie in Ghana, hebben we de compressie van sterfte bestudeerd tijdens de transitie in Nederland en Japan in **hoofdstuk vier**. Onze bevindingen in Nederland en Japan laten zien dat met een toename van de levensverwachting, de spreiding van sterfte over de leeftijd comprimeert. Met andere woorden, de spreiding in levensduur tussen mensen is afgenomen. Daarnaast hebben we gevonden dat er een limiet is bereikt aan de compressie van sterfte zowel in Nederland als Japan. Voor beide landen ligt dit limiet op een spreiding van 12 jaar rondom de leeftijd waarop de meeste mensen komen te overlijden in dat jaar. Dit is in lijn met de huidige theorie over veroudering, dat gezien wordt als een stochastische opeenstapeling van schade over de tijd. De snelheid van deze opeenstapeling kan gezien worden als de snelheid van het verouderingsproces. Doordat veroudering een stochastisch proces is zal er altijd verschil blijven bestaan in de snelheid waarmee mensen verouderen. De compressie van sterfte kan dus nooit gecomprimeerd worden tot nul. In een homogene populatie wordt de limiet van sterfte compressie dus bepaalt door de resterende variatie in de snelheid waarmee mensen verouderen.

Naast de compressie van sterfte, bestuderen we in **hoofdstuk vijf** de compressie van ziekte. Top op heden is er nog geen afname in de snelheid waarmee de levensverwachting stijgt. Dit roept de vraag op of de extra jaren die we leven in goede of slechte gezondheid worden doorgebracht. Onderzoek naar de trends in 'gezonde' levensverwachting in Nederland laat zien dat meer jaren geleefd worden met chronische ziekten, maar dat de jaren die we leven zonder lichamelijke beperkingen en de jaren die we leven in goed zelf-ervaren gezondheid parallel stijgen met de stijging in levensverwachting. De toename van het aantal jaren met chronische ziekten kan deels verklaard worden door een toename in welvaartsziekten als diabetes en hoge bloeddruk, maar ook deels door verbetering in vroege opsporing van dergelijke ziekten om zo middels goede behandeling de lichamelijke beperkingen te voorkomen. Deze studie laat daarnaast zien dat er verschillen zijn tussen mannen en vrouwen. Mannen hebben een lagere levensverwachting dan vrouwen, maar leven proportioneel meer jaren zonder chronische ziekten. Op 80 jarige leeftijd

hebben mannen nog steeds een lagere levensverwachting, maar bestaat er geen verschil meer in gezonde levensverwachting ten opzicht van de vrouwen. Voor zowel mannen als vrouwen geldt dat er aan het einde van het leven een periode van kwetsbaarheid blijft bestaan. Deze periode wordt wel steeds verder opgeschoven naar hogere leeftijden, maar niet verder verkort. Onze observaties sluiten goed aan bij de eerdere bevinding dat de meeste kosten met betrekking tot de gezondheid in de laatste twee jaar van het leven worden gemaakt.

Hoofdstuk zes is bouwt voort op het vorige hoofdstuk. Hierin bepleiten we dat het tijd is voor mensen om zich te realiseren dat er niet alleen een langer, maar vooral ook een gezonder leven in het vooruitzicht ligt. Het is van belang om dat we ons hierop instellen en ons leven en de maatschappij daarop aanpassen.

De toename in levensverwachting zoals besproken in voorgaande hoofdstukken geeft al aan dat sterfte op hoge leeftijd plastisch is. De vraag die nog rest is of dat door verbeterde omstandigheden vroeg in het leven komt, of dat ook een betere omgeving op hoge leeftijd daaraan nog heeft bijgedragen. Op deze vraag wordt ingegaan in **hoofdstuk zeven**. Het is reeds bekend dat de vroege leefomgeving van belang is voor het risico van ziekten op latere leeftijd. Onduidelijk is of verandering van omgeving op hoge leeftijd nog kan resulteren in gezondheidswinst. Om dit te onderzoeken hebben we gekeken naar de sterftetrends in Japan. Japan is uniek, omdat het een versnelde epidemiologische transitie heeft doorgemaakt. Cohorten geboren tussen 1900 en 1920 hebben eenzelfde ongunstige leefomgeving gehad gedurende de eerste levensperiode, maar zijn op latere leeftijd blootgesteld aan een sterk verbeterde leefomgeving. Het geboortecohort van 1920 heeft het langste kunnen profiteren van de betere leefomstandigheden op hoge leeftijd hadden dan ook de lagere sterfte op hoge leeftijd ten opzicht van vroegere geboortecohorten. Daarnaast laat deze studie zien dat zelfs tot op hoge leeftijd sterfte plastisch blijft, een betere leefomgeving resulteert in lagere sterfte. Dit geeft weer dat preventieve maatregelen die geïntroduceerd worden op hoge leeftijd nog gezondheidswinst kunnen opleveren.

Als laatste in **hoofdstuk acht** wordt ingegaan op lichamelijke activiteit, één van de belangrijkste determinanten van gezondheid en sterfte. Vaak wordt gedacht dat meer lichamelijke activiteit altijd beter is voor gezondheid en sterftekansen. De meeste studies waarin dit is onderzocht hebben atleten met de algemene bevolking vergeleken. Dit geeft wel antwoord op de vraag of atleten langer leven dan de algemene bevolking, maar niet of dat door de mate van lichamelijke inspanning komt. De algemene bevolking bevat

immers ook mensen met aangeboren ziektes, waar atleten vaak een selectie zijn van de meest fitte mensen in een populatie. In onze studie hebben we daarom gekeken naar sterfte binnen een groep oud Olympisch atleten uit verschillende disciplines met een lage, middelmatige of hoge mate van lichamelijke intensiteit. Hieruit is naar voren gekomen dat atleten uit een discipline met een hoge mate aan lichamelijke intensiteit geen extra overlevingsvoordeel hebben ten opzichte van atleten uit een discipline met lage lichamelijke intensiteit. Olympisch roeiers of marathonlopers hebben bijvoorbeeld geen lagere sterftekans vergeleken met Olympische golfers. Verder is gebleken dat het beoefenen van een sport met kans op lichamelijke botsingen of lichamelijk contact een verhoogd sterfterisico met zich mee brengt ten opzichte van atleten die actief zijn in sporten zonder deze risico's. Voorbeelden van dergelijke risicosporten zijn bijvoorbeeld turnen, voetbal en polo ten opzichte van zwemmen of tennis. Interessant was dat dit hogere sterfterisico ook op hogere leeftijd, na het vijftigste levensjaar bleef bestaan.

In **hoofdstuk negen** sluiten we af door de belangrijkste conclusies uit dit proefschrift samen te vatten en de mogelijke implicaties van deze bevindingen te bespreken.

CONCLUSIE EN IMPLICATIES

Gedurende de epidemiologische transitie is er een daling van sterfte en vruchtbaarheid en neemt het aantal mensen dat een hoge leeftijd bereikt snel toe. Dit gaat gepaard met compressie van sterfte tot een kleiner leeftijds-interval dat uiteindelijk een limiet bereikt. Tegelijkertijd is er nog geen afname in de snelheid waarmee de levensverwachting stijgt en hoewel meer jaren worden doorgebracht met chronische ziekten, leven we langer in goed zelf-ervaren gezondheid en langer zonder lichamelijke beperkingen. Zelfs op hoge leeftijd blijft sterfte plastisch en dus beïnvloedbaar. Het blijft onmogelijk om de toekomst te voorspellen, maar op basis van de historische sterfte trends kunnen we wel scenario's schetsen op basis van waarschijnlijkheid.

Het is een groot voorrecht dat op dit moment zoveel mensen een hoge leeftijd bereiken in goede gezondheid. Dat dit ook nieuwe uitdagingen met zich mee brengt spreekt voor zich.[20,21] Één van de grootste angsten wellicht is de druk op de arbeidsmarkt.[23] De leeftijdssamenstelling in de populatie is drastisch gewijzigd. Voor het eerst draagt het aantal ouderen proportioneel evenveel bij als het aantal volwassenen en jongeren.[21,23] Onderbezetting en werkeloosheid maken de arbeidsproductiviteit kwetsbaar.[24,25] Op dit moment is de leeftijd waarop mensen zich terugtrekken van de arbeidsmarkt gemiddeld lager dan 60 jaar in de meeste landen.[26] Het verhogen van de pensioenleeftijd zal niet

alleen de druk op de pensioenvoorzieningen reduceren, het zal ook bijdragen aan de onderbezetting op de arbeidsmarkt in de nabije toekomst.[22] Het is van groot belang om onze maatschappij zo in te richten dat het groeiende aantal ouderen langer actief kan blijven en op die manier ook langer een bijdrage kan blijven leveren.

Sterfte blijkt tot op hoge leeftijd beïnvloedbaar. Dit is belangrijk in het kader van preventie. Op dit moment is er nog weinig aandacht voor preventieve maatregelen gericht op ouderen. Alhoewel het aantal ouderen snel toeneemt, is er binnen de geneeskunde nog een gebrek aan zo genoemde *'evidence based medicine'* om ouderen optimaal te kunnen behandelen of preventieve maatregelen in te voeren. In dit kader is het van belang om te noemen dat preventie en behandeling van ziekte anders is bij ouderen dan voor volwassenen van middelbare leeftijd.[27,28] Ouderen hebben vaak meerdere ziekten tegelijk, terwijl volwassenen van middelbare leeftijd vaak maar één enkele ziekte tegelijk hebben.[27] Verder verandert met het ouder worden de fysiologie in het menselijk lichaam, waardoor ook de behandeling soms een ander aanpak vraag dan bij mensen van middelbare leeftijd.[28] In de preventie en behandeling van ziekten bij ouderen valt nog veel winst te behalen.[30]

Uiteindelijk hebben we laten zien dat ziekte en sterfte veranderlijk zijn en dat tot op hoge leeftijd blijven. Laat dit een aanmoediging zijn voor zowel de maatschappij als elk individu om hier maximaal gebruik van te maken.

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LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

Lindenberg, H.J.A. Rolden, **F.M. Engelaer**, D. van Bodegom, T. Puvill, Y. Mysyuk, S. Biggs and R.G.J. Westendorp. Position paper on the third demographic transition. (submitted)

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CURRICULUM VITAE

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