Sex Differences in Middle Mortality

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Oliver Wisser
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Gutachter:

1. Gutachter:

Prof. Dr. Roland Rau

Institut für Soziologie und Demographie, Universität Rostock

2. Gutachter:

Prof. Dr. James W. Vaupel

Max-Planck-Institut für demografische Forschung/ University of Southern Denmark/ Duke University

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Contents

List of Tables

List of Figures

Chapter 1

General Introduction

1.1 Background

As adult humans age their mortality risk increases exponentially. The Gompertz *law of mortality* is the best known parameterization of this exponential increase (Gompertz 1825). The empirical evidence for the *law of mortality* suggests a connection between its slope parameter and the underlying biological aging processes (e.g. Economos 1982). The slope of the increase of adult mortality rates is called the demographic rate of aging (ROA) and is usually higher for females than for males in the same population (e.g. Bongaarts 2005). This is surprising, since it implies that females seem to age faster, even though they live longer in contemporary populations. This paradox can be explained by factors affecting the demographic ROA other than the age decline in physiological function. One factor is heterogeneity, which leads to a selection of robust individuals and a deceleration of mortality rates in the elderly population (e.g. Beard 1959, Vaupel 1979). However, heterogeneity cannot be the main cause for the ROA-longevity paradox, since its effects are only noticeable in the very old population. As a second factor, extrinsic hazards affect the slope of mortality. They serve as the most likely candidate to account for the paradox. Extrinsic risk is most pronounced in the young male population. If extrinsic mortality rates are high, they negatively affect the slope of mortality increase (e.g. Gavrilov & Gavrilova 1991). Therefore, the ROA-longevity paradox may be solved by estimating a reliable expression for extrinsic mortality.

In general, extrinsic mortality is either assumed to be constant (Makeham 1867) or to decline over age (Thiele & Sprague 1871, Heligman & Pollard 1980). Classic mortality models presume a clear partition of total mortality into an extrinsic and an intrinsic component. Whereas the extrinsic component acts predominantly at young age, mortality at old adult age is mainly driven by intrinsic mortality. Extrinsic mortality is assumed to stem from an extrinsic stressor decoupled from the aging process. Fatal events, as a result of such stressors, are a leading cause for

adolescent or young adult mortality and are expressed, amongst others, in high rates of traffic accidents, homicides and suicides. For middle and old adult ages, though, mortality is instead caused by the interaction of extrinsic and intrinsic risk factors. In other words, a similar severe stressor is more likely to be fatal for old as compared to young aged individuals.

1.2 Aim of the Dissertation

The aim of this dissertation is to find a mathematical expression to describe middle and old age mortality. Instead of assuming a classic model, which partitions mortality into an intrinsic and extrinsic component, we assume that extrinsic and intrinsic risk factors interact at middle and old adult age. All-cause mortality may be better described by a middle age component, which is called here *middle mortality* (MM), and a Gompertz component. Both components differ only by the age pattern of extrinsic risk factors. Since intrinsic risk (an abstract expression for the biological process of damage accumulation) constantly increases over age and is probably a human biological universality (Vaupel 2010), extrinsic risk factors account for temporal, cross-cultural, and sex-specific dynamics of the mortality pattern.

The Gompertz *law of mortality* can be interpreted in terms of an age-independent environmental risk interacting with the biological aging process. The aging process leads to a decline in the capability to withstand an extrinsic stressor, which causes an exponential increase in mortality rates. In this case, biological aging can be directly estimated by the slope parameter of the Gompertz function. However, if extrinsic risk factors change over age, the interpretational strength of the Gompertz slope becomes rather complicated. Several studies indicate that beneath the Gompertz shaped mortality component there exists a second age increasing mortality component, which is a result of age changing extrinsic stressors and biological aging.

If extrinsic risk factors change over age, they affect the slope of the mortality curve in a manner similar to biological aging. For example, traffic accident rates decline over age for elderly drivers due to gains in experience, declining mobility and less risk-taking (Hakamis-Blomqvist et al. 2002), whereas the fatality rate of traffic accidents is U-shaped (Massie et al. 1995). Hence, safer driving at old ages

compared to young adult age is outweighed by the increasing fragility (Evans 2001). The decline of involvement rates cannot offset the aging process. Hence, such extrinsic mechanisms may negatively affect the slope of mortality rates. However, the slope of the Gompertz mortality component is usually interpreted as biological aging, whereas an age-independent term accounts for all deaths due to extrinsic risk factors. As illustrated in the example above, the involvement of age-dependent extrinsic risk factors and their interaction with the aging process is not considered in classic mortality models. An important scope of the present study is therefore to emphasize the interaction model of mortality. MM results from the interaction of age changing extrinsic risk factors and intrinsic aging processes. Based on the findings of demographic, epidemiological and physiological studies, age changing extrinsic risk factors may play a central role in shaping the age pattern of death rates at middle and old adult ages. These risk factors are likely to be mediated by behavior (Chapter 5). To evaluate the age pattern of MM it would be optimal to study populations which show different mortality rates due to behavioral risk factors. Two subgroups which differ in terms of risk taking behavior and mortality across time and cultures are males and females. The study of the sex gap is therefore a crucial component of this work to estimate and evaluate the middle mortality model. The thesis is therefore separated into two parts. **Part I** focuses on sex differences in mortality, whereas in **Part II** a middle mortality model is developed and applied to the problematic of the sex differentia in mortality.

1.3 Methodology

Females live longer in virtually all societies and suffer less mortality throughout their whole middle and old adult life compared to men (e.g. Glei 2005). Excess male mortality is mainly attributed to more pronounced reckless behavior and less to biological differences (e.g. Rogers et al. 2010). Moreover, the variation in the mortality sex gap is mainly a result of higher plasticity in male behavior (e.g. Nathanson and Lopez 1987). In order to get an overview of the sex gap, a brief summary of the present knowledge of why women live longer than men is summarized in **Chapter 2**. The sex gap is studied from different perspectives including demography, epidemiology, social science, (bio-) gerontology,

psychology and biology, just to mention the most important research fields. A full review of all these fields would exceed the framework of this study. Hence, only the most important studies are presented.

The age pattern of the male-female mortality gap provides an approximation of MM. There are two ways of comparing male with female death rates, the ratio and the difference. They provide different information on the underlying risk factors. With declining mortality rates the relative difference tends to increase, whereas the absolute difference decreases. An evaluation of the trend of the changing sex gap and its association with shifting mortality patterns is the subject of Chapters 3 and 4 of this work.

Chapter 3 provides an analysis of the sex differential in mortality by means of the ratio and the difference. The ratio is the common measure, whereas the difference is barely considered in studies of the sex mortality differentials. The comparison between the ratio and the difference also concerns basic questions about the interpretational strength of a relative and an absolute measure. Some authors argue that the ratio provides more interpretational strength about the sex differential in mortality (e.g. Boback 2003, Edwards 2007), whereas others doubt this and claim that using both types of measures provides a less unbiased picture (e.g. Hutton 2000, King 2012, Sacket et al. 1996, Tramér & Walder 2005). Both measures, however, have some undesirable characteristics. Whereas the difference tends to decline with low mortality regimes, since it cannot exceed a certain mortality rate, the ratio tends to increase due to a declining denominator. This numerical artifact weakens the interpretational strength of the sex differential and is analyzed in **Chapter 4**.

In order to provide an appropriate mechanistic mortality model, **Part II** of this dissertation provides a methodological perspective on the male-female gap in mortality. **Chapter 5** reviews mortality models and interpretations with special emphasis on the Gompertz model. Moreover, the age pattern of MM is developed based on interacting risk factors and auxiliary information of demographic, epidemiologic and psychological studies. Several of these studies imply that the non-Gompertz component is increasing over age, rather than following a Makeham pattern. Finally, **Chapter 6** provides a mathematical expression, here called the κ-Gompertz model, including a Gompertz and MM component. The κ-Gompertz model provides a good approximation of the changing sex gap in LE in European

countries throughout the past 150 years. The Gompertz-Makeham model is a special case of the κ-Gompertz model. This provides a testable setting of whether MM is involved in the mortality process.

Part I

The Sex Differential in Mortality

Chapter 2

Theoretical Background of the Sex gap in Mortality

2.1 The Sex Gap in the Past and Today

That women live longer than men is well-known and applies to virtually all societies in historical or contemporary populations (Nathanson 1984, Wingard 1984). Exceptions to this trend mainly concern some developing countries where females suffer from higher mortality especially in childhood and during childbearing years (e.g. Gjonça et al. 1999, Heligman 1983, Karkal 1987, Klasen 1998, Langford and Storey 1993, Ram 1993).

The gap was mentioned as early as the 17th century by John Graunt (cited in Lopez & Ruzicka 1983) and might be a biological property of humans. However, the sex gap was not of serious interest in the scientific community and only occasionally mentioned before the mid-twentieth century (e.g. Haviland 1870). Beginning in the 1930s interest in the sex gap began to increase (Ciocco 1940, Logan 1947, Martin 1951, Sowder 1954, Stolnitz 1956, Wiehl 1935, 1938, Yerushalmy 1943). This interest was due to a stunning observation – historical life tables seemed to indicate that the sex gap in life expectancy (LE) started to diverge in the mid-nineteenth century and continued in the twentieth century (e.g. Kalben 2000, Retherford 1975, Vallin 1983). The reason for this was that female LE increased faster than male LE with improvements in living conditions (see Figure 2.1).

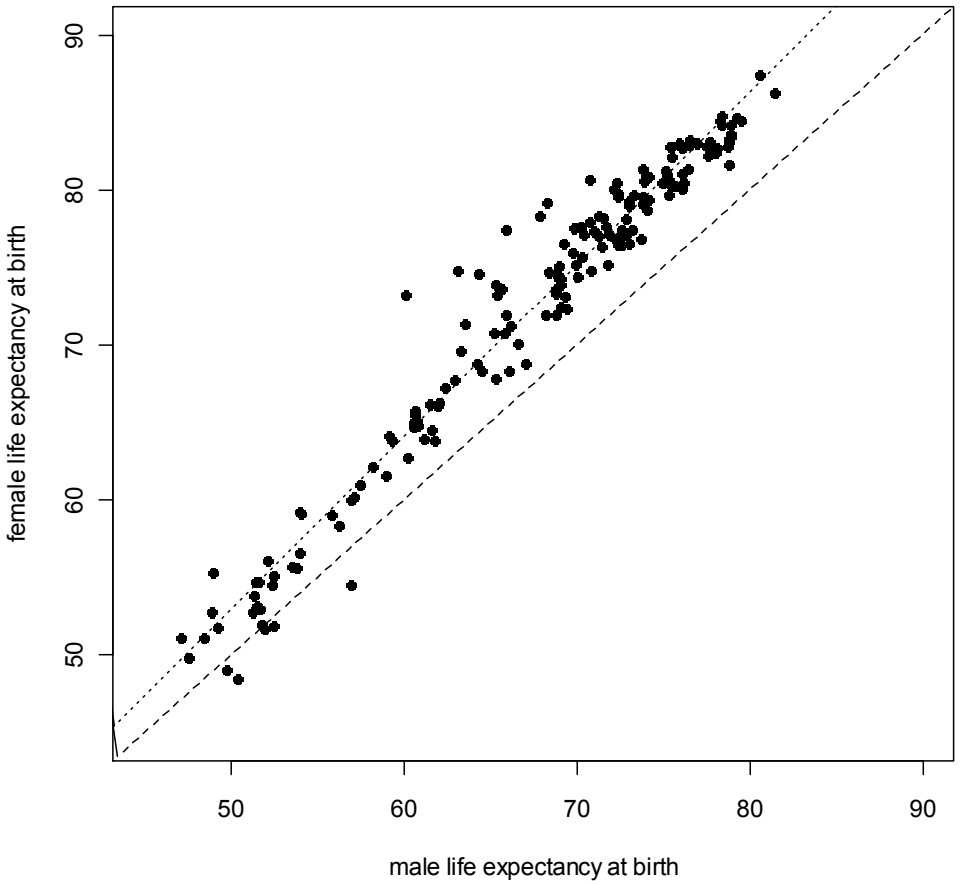

Figure 2.1: Cross-cultural comparison of male and female life expectancy (LE) at birth in 169 countries and territories (source: CIA Factbook 2012). The dashed line reflects equal progression for both sexes, the dotted line the observed progression. For each year of male LE increase, females gain on average 1.12 years (r^2 = 0.9588, $p > 0.001$).

This leads us to ask whether the sex gap is predominantly driven by males or females. The fact, it turns out, is that females benefit more from improvements in living conditions brought about by social and medical developments of the past 150 years. These benefits are not only a consequence of declining maternal deaths, since the divergence of the sex gap in the second half of the twentieth century is mainly due to trends in the 45+ age group (Lopez 1983). A deeper explanation of the gap is grounded in the biological and psychological differences between the sexes. There are two possible explanations of the diverging sex gap: either an increase in living

conditions reveals some biological advantage of females, or males take less advantage of medical improvements due to behavioral and social risk factors. The psychological difference between the sexes may be due to social factors or biological characteristics driven by sex hormones and neurological dissimilarities. In the last couple of decades, ample evidence has shown that the dynamics of the sex gap are mainly caused by males' excessively risky behavior, whereas a small fixed difference might be due to physiological factors leading to higher male susceptibility to several diseases. Given that age-specific variations in male behavioral patterns are a critical factor in shaping age-specific mortality differences between the sexes, any attempt to model human mortality should be based on such findings. However, this has not yet been implemented.

The next sections provide an overview of studies focusing on biological and behavioral differences that explain the sex gap in mortality. Several studies imply that behavioral risk among males is higher than compared to females. Risk taking is not only expressed in accident rates, which account for high male mortality at young ages, but also in fewer doctor visits and sickness reportings, which contributes to the survival-morbidity paradox (women live longer, but suffer more illness).

2.2 Biological Hypothesis

The biological hypothesis proposes that females have a physiological advantage over males. It states that with increasing gender equality and a decline in maternal mortality in the past decades this robustness became more pronounced and accounts for the diverging sex gap. Actually, until the early 1960s it had been assumed that the sex gap in LE was mainly driven by biological differences (e.g. Madigan 1957). An argument for this hypothesis came from the discovery that cardiovascular diseases (CVD) are a major driver of the diverging trend. In the mid-twentieth century CVD has been attributed to biological risk factors (e.g. Enterline 1961). However, nowadays it is assumed that the main driver of CVD mortality is caused by behavioral patterns (Waldron 1976, Wang et al. 2006). This insight is based on several epidemiological studies. Actually, CVD risk, which mainly accounts for the widening sex gap in the twentieth century (Denton and Walters

1999, Lewis and Lewis 1977), is positively related to fat consumption (Lawlor et al. 2001) and cigarette smoking (Preston 1970, Pampel 2002, Retherford 1972).

Nevertheless, a lot of studies suggest that there is also a sex difference in physiology, which may account for a small, but fixed sex gap in LE. The most prominent candidates are sex hormones and the XY chromosome disparity, which both lead to an advantage in female immune functioning (e.g. Austad 2006). For example, studies on vertebrates show a suppressive effect of testosterone/androgens on the immune system (Klein 2000) leading to higher male susceptibility to viral and parasite infections mediated by sex differences in immune functioning (Guerra-Silveira and Abad-Franch 2013, Klein and Huber 2010, Roberts et al. 2001, Zuk and McKean 1996). Beneath the biological explanation, there is also the hypothesis that behavior drives the sex difference in susceptibility to infectious diseases. This is, because risky behavior is also driven by testosterone and may account for or at least exaggerate parasite risk due an increased exposure in the wild (Roberts et al. 2001, Zuk and McKean 1996). However, studies on humans are controversial and may support the biological or behavioral hypothesis. For example, Guerra-Silveira and Abad-Franch (2013) used childhood susceptibility as one of the proxies to test the physiological (PH) or behavioral (BH) hypothesis of sex difference in susceptibility to infectious diseases. They found a higher susceptibility to infectious diseases for males in early childhood when behavior differences between boys and girls are negligible. This interpretation would imply that behavioral differences do not account for the gap and supports the PH hypothesis. However, the results may also be interpreted as supporting the BH hypothesis, since sex differences in susceptibility may be driven by parental care and social status. The authors did not test for social class effects, but this might be important, since they used data from Brazil and other countries they did not specify. If they used less-developed countries then low socioeconomic status may be connected to under-nutrition in infants, which leads to defective immune system functioning (Kau et al. 2011). Since male infants have a higher food demand, the results may be biased. In general, the relative contribution of behavior or physiology to sex differences in response to infectious diseases is still unclear.

In contrast to its immunosuppressive function, androgens may also have a positive effect on male survival. For example, a low rate of endogenous testosterone

in men is connected to high CVD mortality and overall mortality (Araujy et al. 2010, English et al. 1997, Haring et al. 2012, Laughlin et al. 2008, Malkin et al. 2010, Vikan et al. 2009). Since endogenous testosterone levels decline over age, this might lead to higher CVD mortality in older men. However, the mechanical link of sex-hormones and cardiac stress are poorly understood and findings of relationships between sex-hormones and CVD mortality are contradictory (Bell et al. 2013). Hence, it might be that factors other than testosterone mediate the CVD risk in elderly men.

Alike the suppressing effect of endogenous testosterone on CVD risk in men, the female sex hormone estrogen reduces CVD mortality in women (Vitale et al. 2009). In postmenopausal women the protective effect of estrogen disappears, leading to an increase in CVD mortality (Colditz et al. 1987, Rosano et al. 2007, van der Schouw et al 1996, Stampfer and Colditz 1991). However, the mechanisms are not fully understood, since estrogen treatment of postmenopausal women shows controversial results and indicates that only treatments shortly after menopause, but not in older women, have a protective effect (Harman 2014).

The possible explanation for why sex hormones have a protective effect relates to the difference in the distribution of male and female body fat. Androgens lead to abdominal adiposity (common in males), whereas extremity adiposity (common in females) is caused by estrogens. Extremity adiposity seems to have some protective effect that reduces CVD rates in females (e.g. Manolopoulos et al. 2010). Actually, adipose men show a higher CVD risk than adipose women compared with the normal population (Wingard 1990, Karastergiou et al. 2012, Lemieux et al. 1994). Fat consumption may account for a large share of male CVD mortality in the twentieth century, since meat and fat intake increased after the second World War and led to more obesity in westernized countries (Lawlor et al. 2001).

Another important theory supporting the biological hypothesis assumes that the male disadvantage in survival is partly due to the XY-chromosome disparity. Males only have one copy of the X-chromosome in their genome. Therefore, mutations on the X-chromosome cannot be buffered. Due to the fact that many genes in the X chromosome, which are connected to immune functioning, are not expressed on the Y chromosome, this may lead to more immune dysfunctions in males (Migeon 2007). Moreover, the XY-chromosome disparity accounts for

increased immune activity in females giving them an advantage in facing pathogens, but causing a higher susceptibility to autoimmune diseases (Amur et al. 2012, Caruso et al. 2013, Libert et al. 2010).

The mechanisms above are the most important ones for explaining the sex gap in LE due to a biological disadvantage in males. However, it is generally assumed that the biological differences are relatively small and fixed, but may be exaggerated by male behavior which accounts for the plasticity in the LE sex gap (Bird and Rieker 1999, Waldron 1982, 1983b). Moreover, there are several other studies reporting a female physiological disadvantage. One example is that even though females have a lower risk of acute coronary heart disease (ACS), those with ACS suffer higher mortality than males (e.g. Claassen et al. 2012). Following severe trauma, men have fewer complications and lower mortality compared to women (Haider et al. 2009, Sakr et al. 2013). Also mild illnesses measured by doctor visits, hospital stays and self-reported health, are more pronounced in females. This phenomenon is called the mortality-morbidity paradox (Bambra et al. 2009, Gove 1979, Nathanson 1977a, Oksuzyan et al. 2008, Verbrugge 1976a, 1982). A main paradox is likely driven by male psychology rather than by real biological differences, as illustrated in the next section.

2.3 Mortality-Morbidity Paradox

Research on the mortality-morbidity paradox, the observation that men die earlier, even though they are in better health compared to females, became the main focus of the research on the sex gap in the 1960s. Actually, the paradox is mainly due to the fact that females are more likely to report mild conditions, whereas severe conditions are more pronounced among males (Gold et al. 2002, Gove and Hughes 1979, Verbrugge 1976b). Therefore, the main question is to what extent this contradiction is due to physiological differences between the sexes and what part is driven by behavior.

First of all, it has often been assumed that the morbidity gap may stem from doctoral visits due to gynecological and obstetrical causes. For example, by using the Danish health register Juel and Christensen (2008) showed that the paradox for hospital admissions can be fully explained by childbearing. However, females are

still more likely to visit a general practitioner and the sex gap in morbidity still remains when controlling for sex-specific diseases (van Wijk et al. 1992). A possible explanation could be that women encounter frequent gynecological visits from young age on and are therefore more used to report on ill conditions compared to men (e.g. Bird and Rieker 1999, Kaplan et al. 1995).

Actually, several studies found that sex differences in health reporting are due to women's greater willingness to visit doctors rather than to more illnesses (Nathanson 1977b, Verbrugge 1976b). Supporting this, male mortality can be predicted much better by self-reported health condition, whereas for females the association between self-reported health and mortality was not found. This implies that women probably exaggerate their health issues, whereas men are more likely to report only severe health issues, but not mild and non-life threatening ones (Deeg and Kriegsman 2003, Nishi et al. 2012). Also, prescribed activity restrictions are higher for female patients than for males with equivalent characteristics. Causes are sex differences in illness behavior and physician gender, i.e. male physicians are four times more likely to prescribe activity restrictions for female as compared to male patients (Safran et al. 1997). This might be due to patient-physician interaction, as women report worse symptoms than men for the same health condition.

In order to understand why females are more conscious and attentive about their health, and men more dismissive, research has investigated and found that women experience minor illnesses differently than men (Popay et al. 1993), suffer more distress and experience more extreme emotional conditions, such as anger or sadness than men (Mirowsky and Ross 1995). Another psychological measure is the big five personality traits, which measure neuroticism, extraversion, openness to experience, agreeableness and consciousness. Variation in the male rather than in the female big five personality traits is the main cause for cross-cultural variation in a long and healthy life expectancy (Schmitt et al. 2008). Therefore, the different psychological characteristics between males and females might lead to sex differences in responding to mild illnesses. Hence, because males are less likely to communicate their emotional and health status and in consequence make less use of the medical care system, they are likely to drive the sex gap in mortality and lead to seemingly higher male morbidity. In fact, several studies indicate that

disadvantageous male behavior is a driving force for the widening sex gap throughout the twentieth century.

2.4 Behavioral Patterns and the Dynamic of the Sex Gap

Throughout the twentieth century living standards in developed countries steadily improved and the female advantage in LE became more prominent. Since smoking behavior was more pronounced among men, a major part of the diverging sex gap had been attributed to higher tobacco consumption among the male population (Preston 1970, Pampel 2002, Retherford 1972). Actually, half of the sex difference in total mortality between the 1950s and 1980s was caused by high male smoking rates (Waldron 1986). Other risk factors also play an important role in male survival disadvantage. For instance, increased fat consumption probably accounts for the majority of male CVD mortality in the twentieth century in westernized countries, since it is disadvantageous for males, but protective for females (Lawlor et al. 2001, Takata et al. 2013). Other behavioral patterns also contribute to a large part of the sex gap in mortality (Pampel 2001) and account for higher male accident rates (Pampel 2001), severe traffic accident rates (Li et al. 1998), and occupational hazards (Waldron 1990). For example, it has been found that three-quarters of the sex gap in the US population is due to higher rates of accidents, suicides, cirrhosis of the liver, respiratory cancers, emphysema and coronary heart disease among the male population, which are related to violence, fat consumption, stress response and drug abuse (Waldron 1976, Wong et al. 2006).

The sex gap in life expectancy narrowed between the 1960s and the 1990s, though this trend is country specific (Pampel 2002, Nathanson 1995, Trovato and Lalu 1996). The narrowing sex gap in life expectancy is mainly attributed to diverging smoking behavior between males and females and a shift toward a more vegetarian diet (e.g. Brenner and Mooney 1982, Dwyer and Hetzel 1989, Pampel 2002). Declining male tobacco consumption led to a faster mortality decline, whereas an increase in risky female behavior slowed down the mortality decline (Rostron and Wilmoth 2011). This change was mediated by the sex differences in lung cancer mortality (Osann et al. 1993, Pampel 2003, Peto et al. 1992, Waldron 1993). Also, the downward trend of CVD mortality, which began between the 1950s

and 1960s in several westernized countries, is a main contributor to the narrowing sex gap (Dobson et al. 1981, Epstein and Zaaroor 1982, Patrick et al. 1982, Tanaka et al. 1982, Thom and Kannel 1981, Thom et al. 1985). Changes in CVD mortality had often been linked to cigarette smoking (Hummer at al. 1998, Jousilahti et al 1999). However, the link between smoking and CVD mortality is rather unclear. For example, England and Wales had the most successful smoking prevention campaign, but showed the weakest impact on CVD incidence (Rose 1989). A cross-country analysis shows that there is little evidence of a connection between lower smoking rates and declining rates of CVD (Waldron 1993). The connection between smoking and a narrowing sex gap is probably over-generalized, supported by a cross-country comparison that smoking contributes only a small amount to the sex gap, whereas other non-biological factors may play a more important role (Luy and Wegner-Siegmund 2014).

In general, smokers are exposed to a higher risk of all kinds of diseases, such as CVD, lung cancer, respiratory and pulmonary diseases and liver cirrhosis (Hummer et al. 1998). However, smokers more often reveal type A behavior (characterized by recklessness aggression) resulting in several other kinds of unhealthy habits, such as heavy drinking and/or maintaining a heavy workload and higher accident rates (Hummer et al. 1998). Except for lung cancer and respiratory diseases, such habits could be responsible for CVD and liver cirrhosis rather than cigarette consumption. Actually, workload has more detrimental effects on health behavior and CVD risk for males than females, since the latter only report higher stress levels but do not suffer higher CVD mortality (Hibbard and Pope 1993, Jick and Mitz 1985, Sorensen et al. 1985). Type A behavior is more pronounced in men than in women and also causes higher rates of CVD (Waldron 1978).

Other causes of death related to risky male behavior may also play an important role in the converging trend compared to the diverging sex gap, such as motor vehicle accidents, occupational and other accidents, violence and suicides (Veevers and Gee 1986, Waldron 1993, Trovato and Heyen 2006, Wong et al. 2006). Heart disease mortality for non-diabetic individuals declined faster in men than in women throughout the last decades. The risk that diabetic individuals face is much greater. Hence, heart disease mortality risk for diabetic men declined slowly, whereas it actually increased among women (Gu et al. 1999, Natarajan et al. 2003).

This might be an indicator that diet is an important factor in explaining the narrowing sex difference in mortality.

Another explanation for, at least parts, of the narrowing sex gap may be an artifact of life table function. Glei and Horiuchi (2007) illustrate that the narrowing sex gap in LE may be due to the age pattern of the absolute sex difference in mortality rather than sex mortality ratios. This is because the age distribution of deaths is more dispersed in males than in females. Hence, a similar reduction of mortality has more effect on males and the sex gap tends to narrow. Even though this might not be the main cause of the diverging sex gap, it may account for a part of the variation between countries. Finally, the question arises, what underlying factors may account for reckless male behavior. Several studies indicate that males show a higher plasticity in risky behavior induced by environmental factors, such as economic or social status.

2.5 Behavioral Plasticity, Social and Biological Factors

Men show higher variations in life expectancy among different social subgroups in a population than women do. Low social class is a predictor of cancer, external-cause mortality, and total mortality in males, but not in females (Anson 2003, Blane et al. 1990, Fukuda et al. 2004, Millar 1983, Nathanson and Lopez 1987, Saurel-Cubizolles et al. 2009). Moreover, low education is related to higher mortality from lung cancer, respiratory disease, stroke, homicide, suicide and accident among males, but not females (e.g. Ross et al. 2012). Social deprivation has larger effects on total mortality and smoking related diseases in males compared to females (Eames et al. 1993). The within-population trend is also reflected on a cross-country level. For instance, males show higher variations in CVD mortality compared to females (Thom et al. 1985). Hence, socioeconomic status differences in a population promote risky male lifestyles, but barely affect females.

Marriage status may also play an important role in the socioeconomic differences of the sex gap. Marriage has a protective factor for risky male health behavior and mortality, but has no or only a marginal effect for females (e.g. Gove 1973, Sheps 1961, Shurtleff 1955, Zick and Smith 1991). The difference of mortality risk between non-married men of low and high educational classes is much

higher than the mortality risk difference of non-married women of different educational classes (Montez et al. 2009). Moreover, the number of unmarried men is higher in low educational classes (Koskinen and Martelin 1994), which exaggerates the social class differences in mortality between the sexes.

In conclusion, men and women respond differently to their social environment in terms of unhealthy behavior. The variation of mortality difference between the sexes is mainly due to excess male behavioral risk, which interacts with male specific biological risk factors. Whereas biological risk factors are likely to be relatively invariant, behavioral risk depends on several factors, such as socioeconomic status.

2.6 Conclusion

The dynamic of the sex gap across time and between countries, at least since the mid-twentieth century in westernized countries, is mainly driven by male risk factors. Males seem to respond more intensely to their socioeconomic environment in terms of expressing risky behavioral patterns, such as violence, drug abuse and accidents. This leads to higher variation in male mortality between subgroups within populations and explains the variety of the sex gap between populations. The health-survival paradox indicates a male disadvantage in benefiting from the improvement in the medical health care system during the twentieth century caused by sex differences in psychological profile, which lead to an over reporting of minor health issues in women. Biological factors play a minor role, but are likely to be exaggerated by behavior. For example, diet plays an important role for CVD mortality in interaction with sex-specific fat distribution driven by sex hormones. This increases mortality in obese men, but not in obese women. The male sensitivity to several social factors is likely to be the main driver of a temporal as well as cross-cultural variation in the sex differential in behavioral risk profiles. Therefore, the sex differential in mortality provides a direct measure of the interaction between behavioral and biological risk factors, and excess male mortality is suitable as an approximation of MM.

Chapter 3

The Sex Differential in Mortality: A Historical Comparison of the Adult-Age Pattern of the Ratio and the Difference

3.1 Introduction

3.1.1 Sex Differentials in Mortality

It is well documented that in all human populations for which respective vitality data exist male death rates exceed that of females at virtually every single age year. In contemporary developed countries, the male disadvantage is universal throughout the whole lifespan, whereas in various historical and developing countries a female disadvantage is reported especially during childbearing years. The disparity in life expectancy between the sexes has been growing throughout the twentieth century. This diverging trend can partly be explained by the declining rates in maternal mortality. However, a major element is attributable to sex differences in behavior and biology as illustrated in the previous Chapter. Due to these differences, males and females respond differently to changing environments in the outcome of mortality. For instance, primary care, specialty care, emergency treatment, diagnostic services, and annual total charges are all significantly higher for women, whereas mortality is higher in men (Bertakis et al. 2000). It has been found that this is most likely due to a higher incidence rate of non-fatal diseases in women and fatal diseases in men, like cardiovascular diseases, rather than better self-assessment of signs of diseases in women (Case and Paxon 2005). Hence, biological and behavioral factors, which account for a higher rate of fatal diseases among men, in combination with improving health care systems affect the diverging sex gap. In former East-Bloc countries, behavioral risk factors alone account for extensively high excess male mortality. For example, 15 year old Russian males faced a 12.6 year lower life expectancy than females in 2000-09. This is extraordinarily high compared to western developed countries (e.g., Germany: 5 years) and is attributed to an uncommonly high alcohol and tobacco consumption rate among Russian males (McCartney et al. 2010). In general, premature deaths due to risky male behavioral patterns are universal and related to higher rates of

homicide (Gartner et al. 1990), suicide (Möller-Leimkühler 2003), drug abuse (Rehm et al. 2006) and traffic accidents (Wilson and Daly 1985).

Biological sex differences account for some part of this sex gap, but are assumed to be small and temporarily invariant. In contrast, behavioral patterns and environmental conditions are suggested as primary causes for variations in the sex gap between populations (see Chapter 2). However, the specific determinants and interaction effects of all three factors remain unclear (Rogers 2010, Nathanson 1984). In terms of the diverging sex gap, it has been suggested that the widespread introduction of cigarettes, which was socially more accepted and common among males in the first half of the twentieth century, contributed to higher rates of cardiovascular diseases among men and is therefore an important factor for explaining the increase in the sex differential in life expectancy (Waldron 1985). Since the 1980s the gender gap in life expectancy started to converge in westernized countries due to the late effects of increased tobacco consumption among women (Pampel 2003). Actually, smoking accounts for 40-80% of the sex gap in European countries (McCartney 2011).

Since behavioral risk patterns show variation over age - a prominent example is the immense drop in traffic accident rates between young adults versus middle age adults (e.g., Wilson and Daly 1985) -, an age specific measure of sex mortality differentials is useful to highlight certain age groups in which males are exposed to an unusually high risk. This information is important for developing strategies of health and risk prevention and to understand how environmental or social conditions trigger excess male mortality. Even though cause specific mortality data would be ideal to identify sex and age specific differentials in risk factors, this information is often not available or reliable especially for historical data and developing countries. Moreover, cause specific data may be biased by several factors reducing the reliability of death certificates (e.g., Modelmog et al. 1992). The most commonly used method in measuring sex differentials over age in either cause specific or all-cause mortality is the ratio.

3.1.2 The Sex Mortality Rate Ratio in a Historical Context

Documentations of the ratio in male to female mortality rates (RMR) can be traced back to a long tradition of studies of the sex gap. One of the pioneers who reported on increasing age specific RMR in the early twentieth century was Dorothy Wiehl (1938). She first mentioned a diverging sex gap in the twentieth century by means of the ratio in mortality rates. Her findings inspired demographers to focus attention on this topic. In the following decade the ratio has been established as the preferred age specific measure for sex mortality differentials. Yerushalmy (1943), for instance, studied the age pattern of the RMR. He reported that the relative mortality risk between males and females is highest around ages 20 and 60. This 'two humps'-pattern of the RMR is universal in westernized countries in the twentieth century, but rare in nineteenth century Europe (Glei 2005). Based on the first descriptive analysis, researchers focused their attention on the underlying determinants of the diverging sex gap by analyzing the RMR for different subpopulations and causes of death.

For example, Martin (1951) conducted an extensive analysis of the RMR in European countries between the 1870s and the 1940s to identify determinants of the evolving sex gap. He analyzed the ratio of male to female cause, social class and occupation specific death rates. He found that occupational risk was the main driver in young male mortality in the second half of the nineteenth century, especially for industrial workers. With the beginning of the twentieth century safety permanently increased in hazardous working environments which mainly affected young workers, who did most of the manual work. This fact puzzles Martin, since the RMR increased, especially at younger ages. He tried to explain this paradox with rapidly declining maternal mortality. However, even though maternal mortality dropped rapidly, it might not explain the increase of the RMR throughout the twentieth century. Moreover, maternal mortality did not substantially decline anymore in Western European countries after the 1960s (De Brouwere et al. 1998) and cannot explain the increasing RMR at young adult ages throughout the last century. Martin (1951) also found that a very high RMR appears in the highest social class, whereas it was lowest in the poorest class. This is paradox when considering that in the lowest class males had been exposed to more hazardous work. Irwin added an

interesting explanation of these paradoxes in the discussion attached to Martin's article. By considering that the RMR is inversely related to the denominator, the observed phenomenon may be explained, at least in part, by declining mortality rates in the westernized world. Furthermore, it may explain higher RMR in high social classes, since higher classes experience lower mortality rates compared to lower classes. Even though this is a reasonable alternative explanation of the observed trend, Irwin's objections have been mostly ignored in ensuing analyses of the sex differential by means of the mortality rate ratio. The numerical problem always appears when sex differentials in mortality between populations are compared, which differ in their mortality regime. This is also a problem when comparing different age groups within the population. Differences in the RMR may always be affected by differences in mortality levels and, hence, information about differences in sex-specific risk factors can be distorted.

In other fields of research, the different implications of absolute and relative measures were a topic of great importance. For example, Moser et al. (2007) showed that both measures can lead to different conclusions about health inequalities across countries and times. The authors found that for some countries the time change of health inequalities was either positive or negative depending on the form of measure. In medical studies it has been argued, that an absolute measure between control and treatment group is more useful in rational decision-making of medical treatment in clinical practice (e.g. Tramer 2005).

Even though the methodological problem was already mentioned 60 years ago and is debated in epidemiological and clinical studies, the age pattern of total or cause-specific mortality rates by means of the ratio in a historical or cross-cultural context is still the preferred method in recent studies of the sex gap (e.g. Glei 2005, Gjonça, 2005, Kalben 2000, Kostaki, 2011, Sorenson 2011, Yang and Kozloski 2012, Westerling 2003).

The reasons for the unawareness of the numerical problem of the RMR might be manifold. One likely explanation is that the widening of the sex difference in life expectancy throughout the twentieth century perfectly fits into the observation of increasing RMR's. However, Glei (2005) found that the declining sex gap in life expectancy since the 1980s does not fit into the pattern of the RMR in westernized countries. This is not entirely surprising, since the sex difference in life expectancy

is not necessarily proportional to the RMR (Pollard 1982, 1988). Another reason for the uncritical interpretation and acceptance of the RMR might be that it is a simple comprehensible measure which can be easily communicated to a broader public.

3.1.3 The Age Pattern of the Absolute Sex Difference in Mortality Rates

An alternative measure to the RMR is the difference between male and female mortality rates (DMR). This measure, however, is uncommon among demographers and only a few studies report on it. For instance, Stolnitz (1956) studied the general shape of sex differences in age specific survival probabilities, which is equal to the negative of the sex difference in the probability of dying. Western populations between 1920 and 1950 show a bathtub-shaped pattern of the difference; the curve declined from age 0 to age 1 and increased slowly until age 40 and then more rapidly until the oldest age (Stolnitz 1956). This is in accordance with the age pattern of DMR found in the US population in 1910, 1965 (Retherford 1975) and 1980 (Wingard 1984). But what was the pattern in the nineteenth century when the sex gap in life expectancy was relatively small and how is it nowadays in contemporary countries? Did the DMR always increase over age or is its age pattern variable over time like it is for the RMR? These questions have not yet been answered; no comprehensive analysis of the DMR exists so far.

3.1.4 Aims of this Study

A comprehensive study of the age pattern of the DMR is more than overdue. It is not known how the age pattern of the DMR behaves in a historical context. In contrast, the RMR has been extensively studied. It is well known, that its age pattern is very flat and close to one in historical populations, and that it increases throughout the last century. However, this increase may partly be due to a substantial drop in overall mortality levels since the late nineteenth century and, hence, might not only reflect changes in sex-specific risk factors. If both sexes equally benefit from some reductions of risk factors which lead to declining mortality rates over time, this would be reflected by an increase of the RMR. The DMR, on the other hand, is not affected by reductions in overall mortality levels. Moreover, the sex difference in life expectancy, the ‘currency’ of the sex gap, is only poorly related to age specific contributions of the RMR. In contrast, the relation between the DMR and sex

differences in life expectancy is much stronger and approximately proportional (Pollard 1982, 1988).

The present study aims to analyze the age pattern of male versus female mortality rates in a historical context and to compare it to the trend of the male versus female mortality rate ratio to fill in the gap of this underrated topic. For this purpose, the age pattern of the DMR and its historical changes throughout the past 150 years will be analyzed and compared to the RMR patterns. Since this study is mainly descriptive, determinants of the observed age patterns will only be discussed briefly. The focus of the present chapter is on adult ages, and it discusses possible applications in future research.

3.2 Data and Methods

Age and sex-specific, decade-wise death counts (*D(x)*) and person years lived (*E(x)*) from the Human Mortality Database (HMD, 2014) are used to calculate age and sex-specific mortality rates ($\mu_M(x)$, $\mu_F(x)$) as

$$\mu_{M,F}(x) = \frac{D_{M,F}(x)}{E_{M,F}(x)} \qquad (3.1)$$

The absolute difference of mortality rates (*DMR(x)*) is calculated as

$$DMR(x) = \mu_M(x) - \mu_F(x) \qquad (3.2)$$

and the ratio in mortality rates (*RMR(x)*) by

$$RMR(x) = \frac{\mu_M(x)}{\mu_F(x)}. \qquad (3.3)$$

The DMR and the RMR are calculated for three European countries (Sweden, France, England & Wales) in five decades (1860-9, 1900-9, 1950-9, 1980-9 and 2000-9) for single age years from 15 to 90. The decade-wise counts of vitality data start at January 1st of the first year and ends at December 31st of the last year of the respective decade.

Even though the HMD provides data up to 110+, these age groups are excluded from the present study, since population counts rapidly decline after age 90

especially in historical populations. Observed patterns of the sex differentials at very old age might be more due to statistical perturbations rather than real effects.

All calculations and figures were done using the statistical computing software R (version 3.01) and the integrated development environment software RStudio (version 0.97.551).

3.3 Results

3.3.1 The Ratio

The age pattern of the ratio in male to female mortality rates (RMR) is very flat in the 1860s and 1900s. Between the 1860s and 1900s the RMR slightly declines in Sweden, whereas in France and England & Wales (E&W) it slightly increases (*Figure 3.1*). In general, the RMR steadily increases from the 1900s until the 1980s in all three countries. The increase takes place over the whole adult lifespan, but is pronounced in two 'humps'; a steep one around age 20 and a flatter one between ages 50 and 70. At the highest age, the ratio tends to decline and converges to one in all decades.

England & Wales show a slightly divergent time trend in the pattern of the second 'hump' as compared to Sweden and France. Between the 1950s and the 1980s the RMR declines between ages 50 and 70, in contrast to the increase in the other countries. From the 1980s to the 2000s the RMR hardly changes in respect to the first 'hump'. After age 40 the decline in the RMR is much more pronounced.

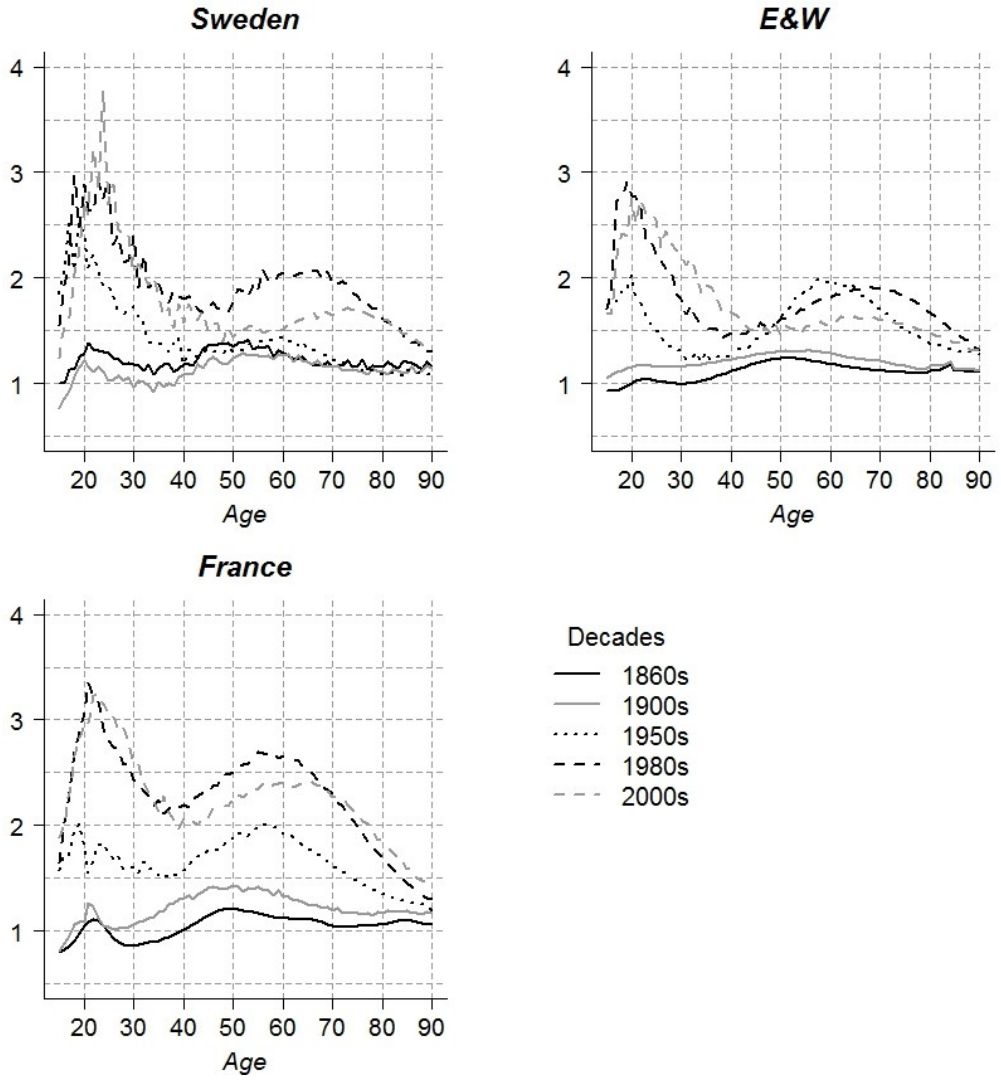

Figure 3.1. Male excess mortality by means of the ratio (y-axis) at single age year between 15 and 90 (x-axis) in three European countries.

3.3.2 The Difference between Ages 15 and 40

Figure 3.2 shows the excess male mortality through the difference between ages 15 and 40. Even though the age pattern of the DMR varies over time, the age pattern across countries is quite consistent. In the 1950s, 1980s and 2000s the age pattern is very flat (between 0 and 0.001) with an increasing trend between ages 15 to 20, and very similar in all countries.

In the 1860s and 1900s the age pattern of the DMR reveals an increase of male excess mortality with a peak roughly around age 20, then declines until age 30 when it starts to increase again. The level of the RMR differs, whereas the age pattern is generally similar, even though it is differently realized among the three countries.

In Sweden, the difference is relatively high in the 1860s compared to the other decades and peaks at age 21 with a value of 0.002. In the 1900s, the shape of the age pattern of the difference is similar to that in the 1860s, but shifted downwards by approximately 0.001.

In France and in England & Wales the difference increases from the 1860s to the 1900s. In 1860s France, female mortality exceeds that of males in every single age year except for ages 19 to 25. Around these ages, the DMR is characterized by a peak with a maximum around 0.001 at age 22. From the 1860s to the 1900s the DMR shifts upwards, with the lowest change around younger ages (0 to 0.0025). However, the general age pattern is entirely preserved.

In 1860s England & Wales, the difference shows a similar shape compared to France, but with a less pronounced and lower peak at age 23 (0.00037). In the 1900s the hump-shape is almost smoothed out and the difference is higher at each single age year compared to the 1860s.

Throughout the second half of the twentieth century the level of the DMR hardly changes. The only evident change is that there is a slightly declining trend in Sweden and France, whereas in England & Wales the DMR is relatively constant in the three latest decades.

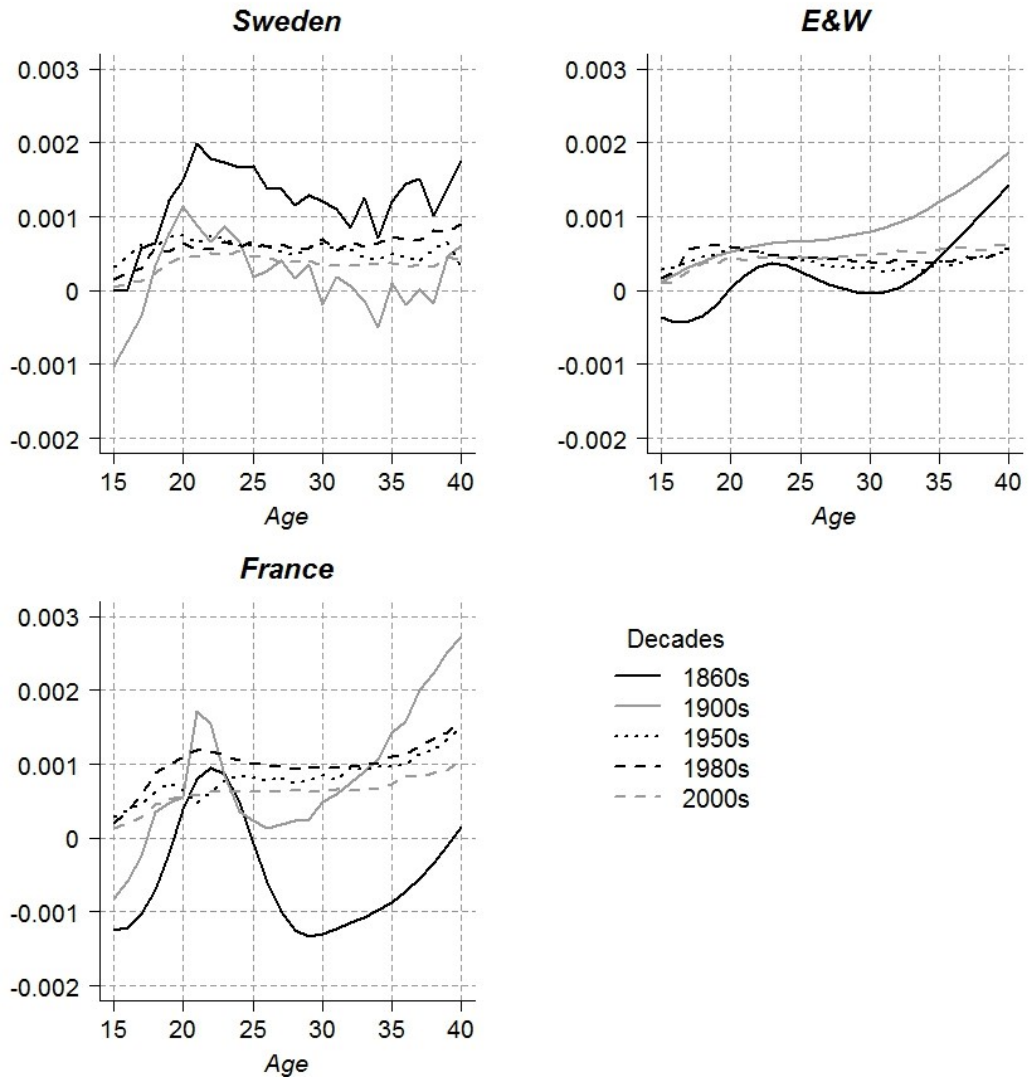

Figure 3.2. Male excess mortality by means of the difference (y-axis) at single age year between 15 and 40 (x-axis) in three European countries.

3.3.3 The Difference between Ages 40 and 90

Figure 3.3 shows excess male mortality by means of the difference between ages 40 and 90. The semi-logarithmic scale is chosen to highlight differences between the decades, which is not possible to such an extent on an arithmetic scale. First of all, the DMR ranges by a factor of 100 over the whole age range, showing an approximately exponential increase in all three countries and over all decades. Historically, however, there are slight differences in the age pattern of the DMR, though these trends are fairly similar across the countries.

For the decades 1950-9, 1980-9 and 2000-9 the age pattern is almost a straight line on a semi-logarithmic scale. There is however, a tendency of a bending off at high age. This is most extreme in England & Wales where the bending off starts earlier than in any other country.

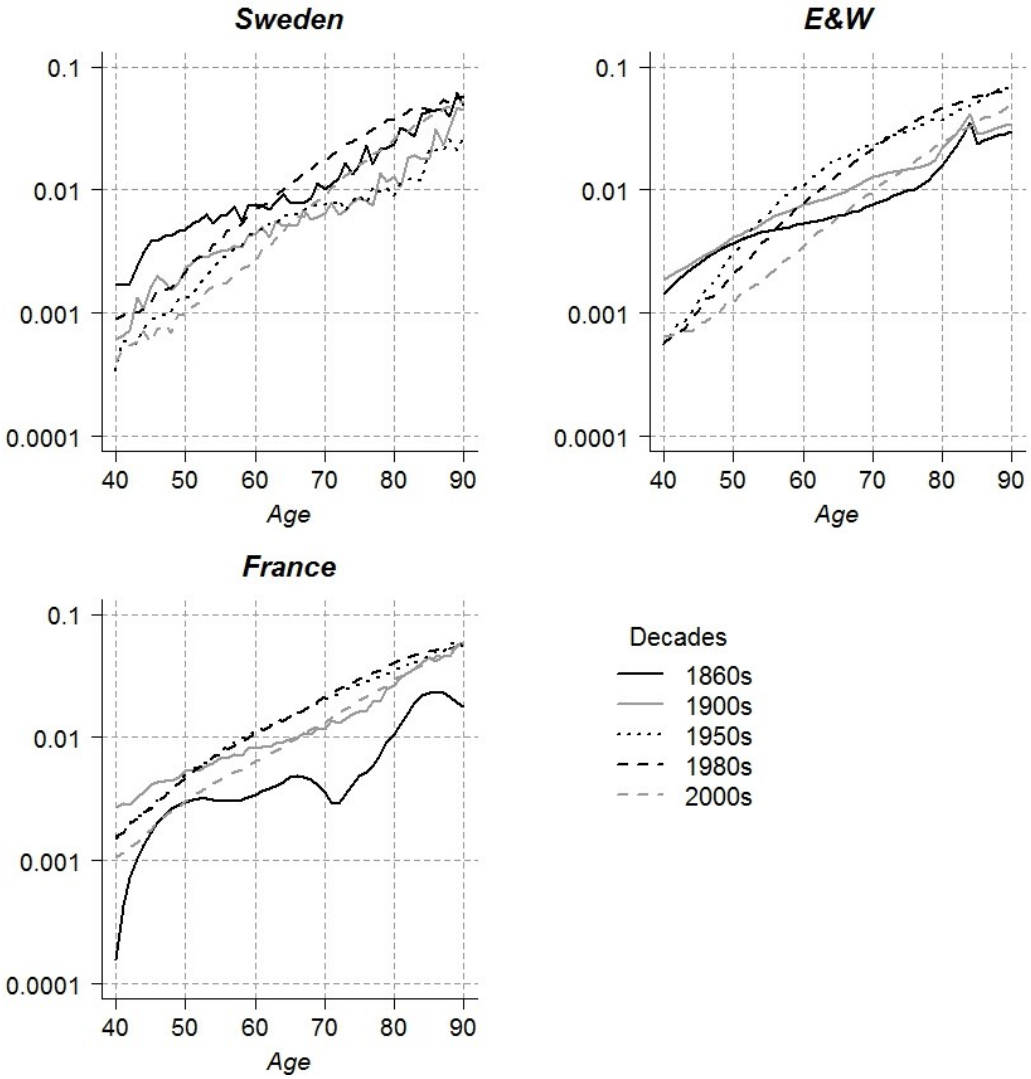

Figure 3.3. Male excess mortality by means of the difference (y-axis) at single age years between 40 and 90 (x-axis) on a semi-logarithmic scale in three European countries.

The straight-line pattern of the DMR at middle to adult ages cannot be found in any country prior to the 1950s. Even though the DMR is increasing over age in the decades 1860-9 and 1900-9, its age pattern is characterized by an inversed s-shape. However, in 1860s France the age pattern of the DMR is very erratic. Even

though the curve is clearly increasing, it does not show an exponential or inversed s-shape pattern. Moreover, the increase of the DMR over age is disrupted by declining trends for ages 65 to 72 and after age 85. In 1900s France, the DMR is much smoother over age and characterized by an inverted s-shape as reported for the other countries.

From the 1860s to the 1900s the DMR drops approximately parallel in Sweden, whereas it increased in England & Wales and France. The shift in England & Wales is not entirely parallel, but the inverted s-shape pattern remains. Moreover, a unique peak of the DMR in England & Wales appears at age 84. This is due to data issues. Annual numbers of deaths and population counts were summarized in the open age interval 85+ in the original tables. To get single age year estimates, deaths and exposures for age above 84 have been calculated by the Kannisto-model for old age mortality (Thatcher et al. 1998). For further information see the method protocol for the HMD by Wilmoth et al. (2007).

In 1950s Sweden, the DMR also shows an inverted s-shape over age in contrast to the other countries. Moreover, at ages above 55, the DMR in Sweden is even similar to that in the 1900s.

Whereas the shape of the age specific DMR pattern is equal in all countries from the 1950s to the 2000s, its temporal change differs between the countries. In Sweden, the DMR increases from the 1950s to the 1980s at each age. In contrast, in England & Wales the DMR slightly declines from the 1950s to the 1980s between ages 40 and 70, but slightly increases at higher ages. There is no change in the level of the DMR between 1950s and 1980s France. After the 1980s all countries shows a rapid substantial decline of the DMR.

3.4 Discussion

The age pattern of the sex differential by means of the ratio substantially differs from that by means of the difference. The most striking finding is that the DMR increases from middle to old age (40 to 90) in all decades and countries in the study. Moreover, in the three last decades the curve of the DMR is clearly exponentially increasing and bends off at old age, except for 1950s Sweden. The bending off may be explained by selection processes. Since males suffer from higher

mortality, the proportion of frailer individuals declines faster in the male population compared to the female population. The increase in the DMR is slowed down at higher ages. This effect "may be a factor in observed declines and reversals with age of mortality differentials between pairs of population" (Vaupel et al. 1979, p. 440). The explanation for the exponential increase is, however, more challenging. In the nineteenth and early twentieth century the age pattern of the DMR describes an inverse s-shape curve rather than a straight line. Hence, two DMR-specific curve-types can be found in all three countries in the present study. The irregular pattern in 1860s France is due to a cohort effect. As shown in Figure 3.4, the cohort effect traces back to the 1770s and 1790s birth cohorts. This is a rare and remarkable example of female excess mortality throughout major parts of the adult lifespan. This pattern might be linked to the devastating crop failure and famine in 1788-89 and the following French Revolution. The years around the 1770s are also characterized by riots due to food shortages. However, shocks, such as malnutrition in fetuses or early infancy, are only weakly related to mortality in adult life (Roseboom et al. 2001, Myrskylä 2010), and a female disadvantage in late life due to famines has not been reported so far. An alternative explanation might be that early shocks led to a stronger selection among males due to a higher infant mortality than in females. However, these are only speculations, and so far there is no explanation for the excess female mortality in the 1770s and 1790s cohorts in France. This observation therefore needs further examination in future studies.

Since the age pattern of DMR at adult ages (40-90) is quite stable over time (except for the special case of France) the underlying mechanism leading to this pattern should be universal. A possible explanation is that biological risk factors account for this trend, since sex differences in biological risk factors are assumed to be fixed and invariant over time (Seifarth 2013). Hence, biological risk factors seem to be good candidates for driving the age pattern of the DMR. However, biological differences are not only fixed, but also small (Rogers et al. 2010). For example, Luy (2003) found that monks and nuns in cloistered populations, which share a similar life style, have a life expectancy gap of approximately one year. The author concludes that this difference is mainly attributed to biological differences. So why is the age pattern of the DMR invariant over time, if the temporal dynamic of sex gap in mortality is mainly driven by behavioral patterns?

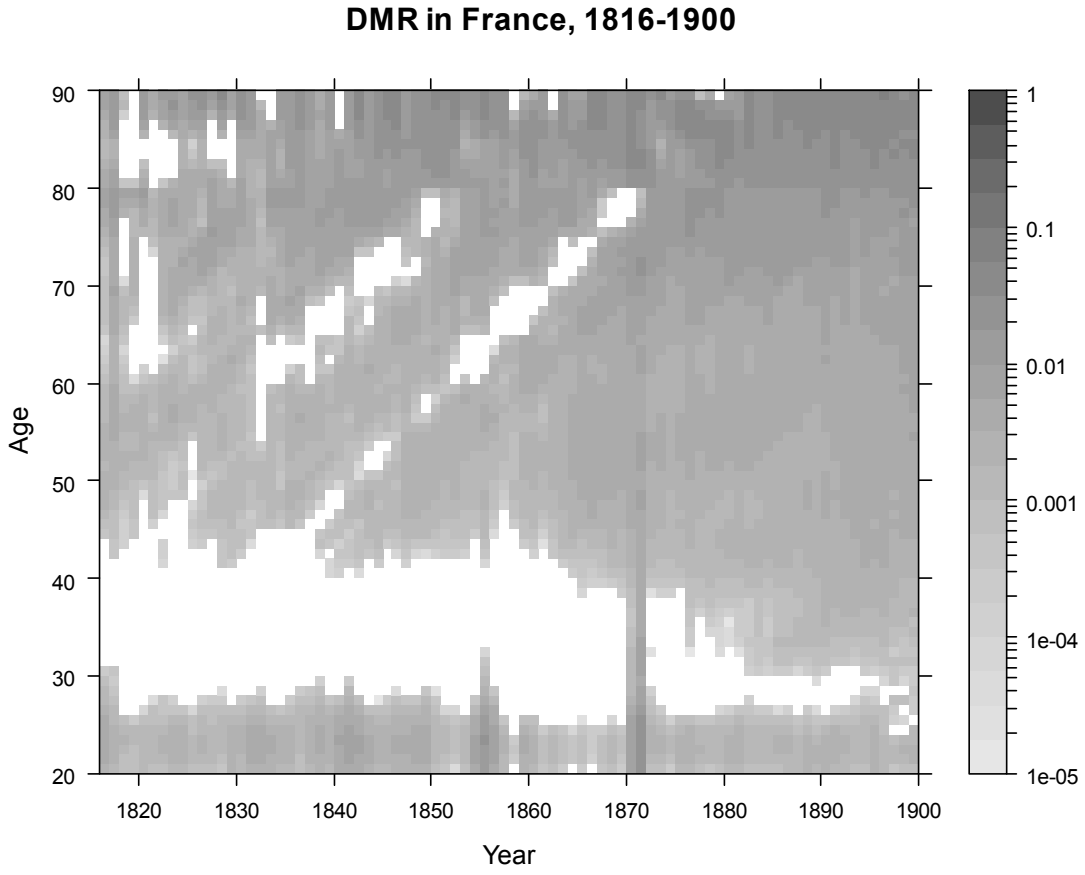

Figure 3.4. Male excess mortality by means of the difference represented by gray shades over single age years and period years. White areas indicate female excess mortality. Two cohort effects can be identified; one in the 1790s and one in the 1770s cohort. Both effects account for an irregular trend of the DMR in the 1860s France.

A possible explanation can be found when considering the complexity of death events. Even though biological sex differences are fixed, environmental and behavioral risk factors can lead to an exaggeration in sex mortality rate differences due to interactions with physiological aging processes. In simpler words, a risky behavior at old age is more likely to be fatal compared to the same behavior at a young age. With increasing age, environmental and behavioral risk factors have more impact on the chance of dying due to physiological aging processes. If women

behave less risky, then their probability of mortality – as compared to that of men – increases more slowly from each single age year to the next. Hence, the mortality gap diverges over age, even though biological differences can be small or even absent. Therefore, the exponential increase in DMR might be solely attributed to sex differences in behavioral and environmental risk factors. Variations over age in the level or shape of the DMR-curve may be a result of temporal changes of the age pattern of such risk factors. A good example is the rate of fatal traffic accidents per mile driven. The chance of an accident declines from young age to middle age, but after a certain age it starts to increase again and even exceeds that of younger ages (Wilson and Daly 1985). Since this pattern is unlikely to be caused by higher risk taking among the elderly, lower reaction times and higher frailty are possible determinants.

In contrast to the age pattern of the DMR, the RMR is flat in the 1860s and 1900s and 'two hump'-shaped in the three latest decades, as already documented by several other studies. Moreover, the RMR implies that the mortality differential has been growing throughout the twentieth century at each specific age. This is, however, not supported by the absolute sex difference in mortality rates. For instance, the DMR in Sweden is much higher in the 1860s between age 17 and age 60 compared to all other decades in the study. In contrast, the RMR in the 1860s is flat and does not exceed the level at any single age in the 1980s and 2000s. Actually, male mortality was generally very high due to alcohol consumption and tuberculosis (Fridlizius 1988) in historical Sweden. Between ages 15-40 the DMR shows a typically 'hump'-shaped pattern in the 1860s and 1900s, whereas the age patterns in later decades are flattened out. The 'hump'-shape is likely linked to maternal mortality. In contrast, the RMR shows a temporarily reversed age pattern. It is flat in the two oldest decades, but 'hump'-shaped in the three latest ones. Additionally, the DMR at young ages tends to decline in two of the three countries (Sweden and France) throughout the twentieth century, whereas the ratio clearly increases in all countries. This might be an artifact of declining mortality levels in the population, because the RMR increases with a declining denominator.

The numerical problem is also likely to account for inconsistencies of the relative proportion of changes in the RMR as compared to the DMR. For the age group 15-40 the biggest changes in the DMR take place between the 1860s and

1900s, whereas the biggest changes in the RMR for the same age-span take place from the 1900s until the 1980s. The increase of the RMR can, at least in parts, be explained by the rapid drop in mortality rates of both sexes with the beginning of the twentieth century rather than by a divergence of sex-specific risk factors. Therefore, the ratio has to be handled cautiously when interpreting sex differentials in a historical context.

However, a numerical problem also appears by using the DMR, since excess male mortality cannot exceed female mortality rates. Hence, the exponential increase of the DMR over age might simply be due to increasing mortality rates. Similarly, the declining trend of the DMR over time might be due to declining mortality rates. For instance, Boback (2003) shows that the mean DMR (ages 35-69) is directly proportional to male and female mortality combined among 32 contemporary countries. However, not all patterns of the RMR or DMR may be explained by numerical issues. For example, in France and England & Wales the DMR increases from the 1860s to the 1900s in the age group 15-40, although total mortality declines. The increase must therefore be linked to sex-specific risk factors, possibly related to shrinking maternal mortality. The RMR, on the other hand, increases from age 40 to 60 in most westernized countries, even though the denominator also increases. There has to be a clear male risk factor which accounts for this trend. Nevertheless, a measure which corrects for mortality levels in a population allows to distinguish between numerical effects and sex-specific risk factors and provides a promising outlook on future research on the determinants of the sex gap.

3.5 Conclusion

The ratio (RMR) is the standard measure of sex differentials in mortality. It is commonly known that the RMR is historically small and increases throughout the twentieth century. However, numerical properties might account for the trend in the RMR rather than sex differences in risk factors. This chapter examines the age pattern of the absolute difference in male to female mortality rates (DMR) as an alternative measure in a historical context and compares it to the RMR pattern. Whereas the RMR is close to one at every age in the nineteenth and early twentieth century and increases until the present day, the adult age pattern of the DMR is

relatively stable throughout the last 150 years. It is also shown that the DMR is approximately exponentially increasing from age 40 to 90, implying a universal biological force behind sex differentials in mortality. However, interactions between biology, behavior and environment are complicated and have to be considered when interpreting these findings. Moreover, between ages 15 and 40 the DMR declines in the second half of the twentieth century, whereas the RMR increases. Hence, the trend in the latter measure is likely to be an artifact of very different mortality regimes between populations. Therefore, it is necessary to consider both measures when conducting comparative analyses and to be careful in interpreting their time, cross-cultural and age trends, since they can lead to different conclusions about sex-specific underlying risk factors.

Chapter 4

The Changing Sex Differential in Mortality as a Function of Total Mortality

4.1 Introduction

The sex differential in mortality is a well-studied, but less well understood phenomenon (Lopez 1983, Regan & Partridge 2013, Waldron 1993). In virtually all contemporary and historical populations women live longer than men (Medalia & Chang 2011) and male mortality exceeds that of females' at most adult ages (Glei 2005). The historical evolution of the sex gap is of special concern in order to evaluate the biological or behavioral causes for the male disadvantage. Generally, there is strong indication that the sex gap is mainly driven by environmental and behavioral risk factors, although biological differences may exacerbate risk factors (see Chapter 2).

Reports on the age specific sex gap in mortality usually include the mortality rate ratio, but not the mortality rate difference (see Chapter 3). Whereas the former measure provides information on the relative disparity between sexes, the difference reveals the absolute size of the sex differential. A main reason for the bias towards the ratio in the sex gap literature is that risk factors are usually assumed to affect a baseline hazard shared by both sexes proportionally. Following this assumption, the ratio directly reflects sex-specific underlying risk factors. In contrast, reporting absolute differences is more common in medical studies for the purpose of an economic cost-benefit calculation of a treatment on a population level. However, the absolute difference is assumed to provide less information for the interpretation of group differentials in mortality (e.g. Edwards 2007), even though this has been critically questioned (e.g. King et al. 2012). Therefore, many authors prefer ratios for examining time trends of the sex gap in order to get insights into causational relationships (e.g. Wingard 1984). Another strong argument for using relative instead of absolute measures is that the latter are limited to male mortality rates. In populations with low mortality rates, the difference is expected to be smaller than in populations with high mortality solely due to the fact that the absolute sex gap

cannot exceed male mortality rates. However, if some risk factors similarly affect both sexes, the ratio is also driven by the mortality regime rather than by sex-specific risk factors.

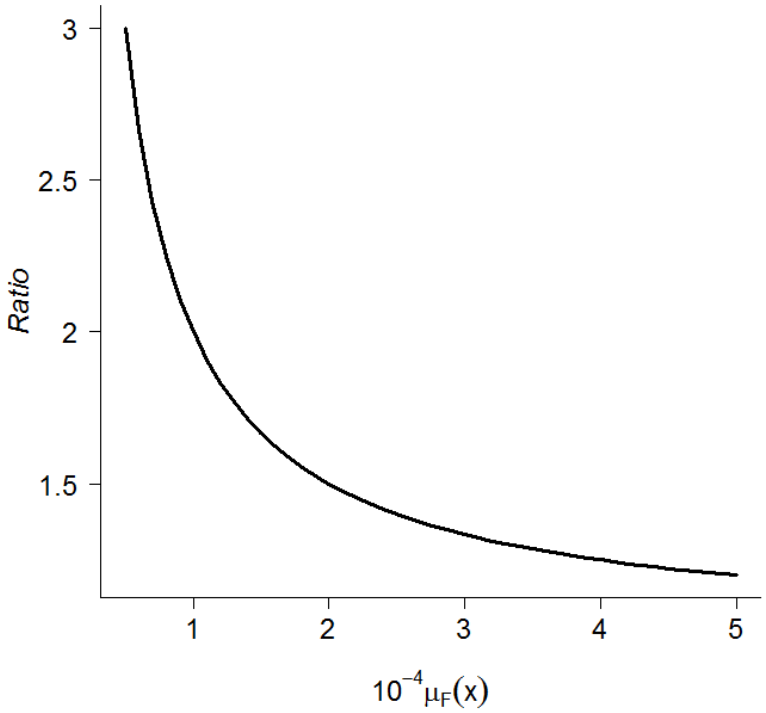

Figure 4.1. Change in the ratio of mortality rates between sexes (RMR) (x-axis) versus female death rate (y-axis), if the absolute difference in mortality between males and females (DMR) stays at a constant level of 10^{-4}. If the DMR does not change and mortality declines, the RMR is solely a function of either male or female mortality. To simplify, one can also express the RMR as a function of total mortality. The RMR is sensitive to total mortality, especially if mortality rates drop to low levels.

A simple illustration elucidates this problem. Let us assume that both sexes are equally exposed to the same event and that the fatality of this event depends on sex-specific risk factors, either environmental or biological, and that these sex-specific risk factors fully account for the sex gap. The ratio provides a tool to indirectly measure and draw conclusions about these risk factors. However, there are risk factors which do not or only marginally discriminate between the sexes. If sex-unspecific risk factors are relatively high and they are the driving forces of mortality

decline over a time period, they mask sex-specific risk factors. Hence, by using a relative measure to analyze time trends of the sex differential in mortality, one might draw the wrong conclusions about the underlying mechanisms in sex-specific risk factors. This is due to the simple reason that the ratio changes with the denominator, and this leads to an overestimation of the sex gap in populations which suffer from relatively low mortality levels. A simultaneous change in male and female mortality with the same difference of mortality rates (DMR) leads to an increase of the ratio in mortality rates (RMR), as illustrated in Figure 4.1.

This leads to the question of how meaningful the ratio and the difference are in explaining underlying risk factors, which drive the sex differential in mortality. Even though the DMR is not affected by sex-unspecific risk factors, the sex gap will be underestimated, since the DMR cannot exceed total mortality rates. This leads to the dilemma, that both measures are characterized by undesirable properties. The dilemma is well known and highly debated in medical studies, since it leads to important decisions in medical treatments and economic considerations (e.g. Hutton 2000, Sacket et al. 1996, Tramér & Walder 2005). The majority of the studies concerning the sex gap in mortality, though, report on relative differentials, whereas only a few studies report on absolute sex differentials, and never considering the methodological problem. It is often stated that the debate about relatives and absolutes is a pure semantic problem (e.g. Edwards 2007). However, this would only be true if there was no interest in studying the underlying sex-specific risk factors driving the trend in the relative or absolute sex gap.

In order to provide a justification for using either the RMR or the DMR, the present study examines the strength of the association between the relative or absolute sex gap in mortality and the mortality regime in the adult population over age and time.

4.1.1 The Time Dimension

Mortality rates in western populations dropped dramatically in both sexes, in young age groups even more than 99%, throughout the past 150 years (Burger et al. 2012) due to the epidemiological transition (Omran 1971). Additionally, the sex gap underwent country specific changes in the past. In order to account for these changes, it is necessary not only to analyze the evolving sex gap between the

nineteenth century and the present, but also to study the sex gap within certain time periods. Figure 4.2 shows the development of the sex gap in life expectancy at age 18 in Sweden, France and England &Wales (E&W), which serves here as a proxy to identify the different temporal subdivisions used in this study.

Concerning its time trend (Figure 4.2), the sex gap can be separated into three distinctive periods:

I. The **pre-World War II period**, which is characterized by a slowly increasing sex gap (e.g. Stolnitz 1956);

II. The so-called **'smoking epidemic'**, characterized by the accelerated widening of the sex gap (e.g. Nathanson, 1984; Waldron, 1993);

III. The **post-'smoking epidemic'**, which captures the last two to four decades, depending on the country, and is characterized by a converging trend (e.g. Trovato & Lalu, 1996, 1998).

Moreover, the disparity between young and old age mortality in westernized populations increased due to the ongoing epidemiological transition in the second half of the twentieth century (Tuljapurkar et al. 2000). Hence, it is likely that the RMR and the DMR are driven by different contributions of sex-specific and sex-unspecific risk factors at different ages. In order to account for this fact, the time dimension is separately analyzed for young, middle and old adult age groups.

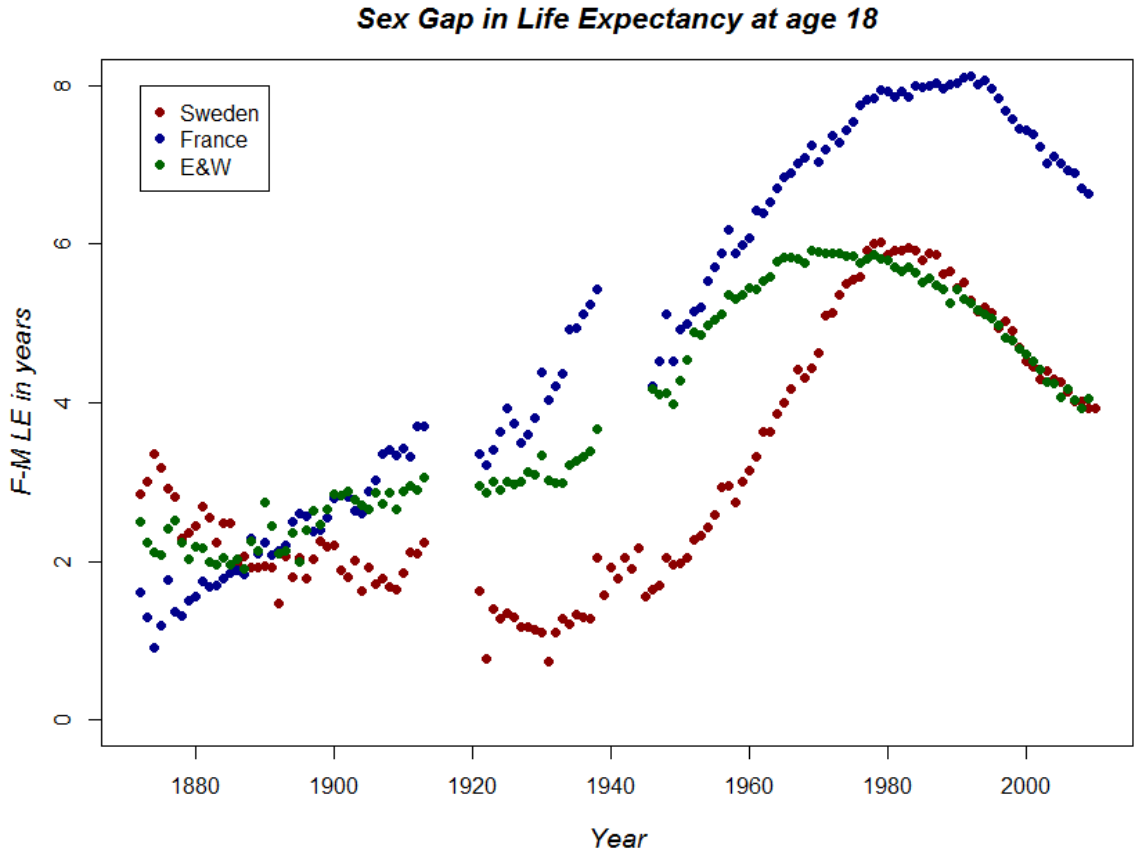

Figure 4.2. Female minus male Life Expectancy (M-F LE) at age 18 in three European countries (Sweden, France, England & Wales) between 1872 and 2010 (periods 1914-1920 and 1939-1945 excluded due to the World Wars and the influenza epidemic). In Sweden, the first time period is characterized by a declining sex gap mainly due to the reduction of excessive alcohol consumption in the male population (Fridlizius 1980).

4.1.2 The Age Dimension

The distinction between biology and environment is a key focus of studies of the sex gap. The sex gap over age reveals the impact of sex differences in biology and environmental risk factors on mortality. Old age mortality is mainly driven by biological risk factors, whereas extrinsic risk factors affect mortality rates predominantly at young ages. Since mortality rates increase exponentially and can differ up to a thousand times between young and old adult age groups, the RMR tends to decline, whereas the DMR tends to increase over age (see Chapter 3). This could weaken the conclusions about the impact of possibly involved biological and environmental risk factors. Hence, it is necessary to determine the role of age-specific mortality as a driver for the relative or absolute measure of the sex gap in mortality.

4.1.3 Aims of the Study

Comparisons of the DMR or RMR between populations with different mortality regimes appear to be problematic. Measuring the historical mortality sex gap either way does not necessarily provide insights about how underlying sex-specific risk factors have changed over time. A possible method for dealing with this issue is to express sex differentials in mortality as a function of the mortality level in a population. Boback (2003) applies this simple idea to evaluate cross-cultural sex differentials in mortality by means of the difference and the ratio of 32 European countries. He finds that the age standardized absolute difference between age 35 and 65 is positively correlated with the mortality rate of the combined sexes, whereas the ratio was not associated with total mortality. Based on these findings, Boback concludes that a relative measure of the sex gap is more meaningful in reflecting underlying risk factors compared to an absolute measure. The correlation between the DMR and overall mortality is especially due to the numerical artifact that rate differences cannot exceed total rates. This phenomenon is an essential problem when studying modern societies which show low levels of mortality. Historically, mortality rates were much higher and may have had less impact on the DMR. Hence, Boback's findings might be special cases which apply to modern societies, but little is known about the historical context. Moreover, Boback assumes the

relationship between the RMR and total mortality to be linear. However, the RMR must be assumed to be inversely related to mortality rates, as illustrated in Figure 4.1.

There are several possible scenarios for the association between the DMR or the RMR with mortality rates. In the present chapter, the following scenarios will be quantitatively tested by estimating these measures on a time and age dimension:

- A negative or negligibly small correlation implies some explanatory strength of the respective measure, since in such a case sex-specific changes in risk factors offset or even counteract the numerical property.
- If the measure of the sex gap is positively correlated to the mortality regime, it possibly means that the respective measure poorly reflects changes in sex-specific risk factors. In consequence, this would mean that the trend in the DMR and RMR is likely driven by sex-unspecific risk factors.
- If the measure of the sex gap is positively correlated to the mortality regime, this could also mean that sex-specific risk factors affect the DMR or the RMR in the same direction. For example, mortality declines due to medical improvements affecting both sexes equally. This would increase the RMR. There is, however, a male-specific risk factor, which increases simultaneously. The RMR would therefore increase faster than expected from the numerical property.

4.2 Data and Methods

Age- and sex-specific as well as decade-wise death counts (*D(x)*) and person-years lived (*E(x)*) from the Human Mortality Database (HMD, 2014) were used to calculate age- and sex-specific mortality rates, μ, for single age years, x, as well as the age standardized crude death rates (ASCDR) for the age groups 18-39, 40-64 and 65-89.

$$\mu_i(x) = \frac{D_i(x)}{E_i(x)}; with\ i = M, F\ (M = Males, F = Females) \qquad (4.1)$$

The absolute difference of mortality rates (*DMR(x)*) is calculated as

$$DMR(x) = \mu_M(x) - \mu_F(x) \qquad (4.2)$$

and the ratio in mortality rates (*RMR(x)*) by

$$RMR(x) = \frac{\mu_M(x)}{\mu_F(x)}. \qquad (4.3)$$

First, the association between the relative or absolute sex differential and the total mortality in the adult age population is analyzed in a historical context of three Western European countries: France, England & Wales (E&W) and Sweden. All three countries are characterized by both common and unique changes in socioeconomic or cultural environments. The oldest well-documented sex-specific vitality statistic dates back to 1751 Sweden. In order to find a common starting year for the analysis, though, the following facts are taken into account: Since age heaping due to misreporting and other problems does not allow for sufficient data quality before the mid-nineteenth century, the data quality in Sweden before 1861 and in E&W before 1868 is insufficient for a quantitative analysis. In France, the Franco-Prussian War, which lasted from 1870-71, had a huge impact on French male excess mortality. Hence, the earliest possible starting date for all three countries with acceptable data quality and no impact from wars is 1872. Moreover, the time periods 1914-20 have to be excluded due to World War I and the influenza pandemic, and the calendar years 1939-45 have to be excluded in France and E&W due to World War II.

The correlation analyses are performed for three different time periods, which are characterized by different dynamics of the sex gap in LE: A pre-World War II period and two post-World War II periods. The sex gap in LE has widened since the late nineteenth century in E&W and France and diverged even faster after the Second World War (Figure 4.2). In contrast, Sweden is characterized by a converging trend of the sex gap until 1931. After 1932 the sex gap started to widen in Sweden and followed a similar trend as observed in France and E&W. In order to divide the post-World War II period, the year of the largest sex gap is selected as the boundary between the ‘smoking epidemic’ and the post-‘smoking epidemic’ period (Figure 4.2). For each of these time periods as well as for the whole time span it is analyzed to what extent the DMR and the RMR changes with total mortality rates. Based on the above criteria, the following time periods are selected:

Sweden: 1872-1931 (1914-1920 excluded), 1932-1979, 1980-2010

France: 1872-1938 (1914-1920 excluded), 1946-1992, 1993-2010

England & Wales: 1872-1938 (1914-1920 excluded), 1946-1969, 1970-2010

Secondly, the relationship between age specific total mortality rates and the RMR or the DMR is analyzed. For this, the extent to which this relationship changes across the time dimension will be examined.

Linear regression analyses are applied to identify the association between total mortality rates and the historical change in the sex differential and to identify the association between total mortality rates and the age change in the sex differential, the DMR or RMR. The linear regression is defined as

$$y_i = A + Bx_i + \varepsilon_i; \text{ with } i = 1, \dots, \text{n}$$

with y_i being the dependent variable which responds to the independent variable x_i with a certain relationship denoted by A and B.

Concerning the time dimension, a linear relationship is assumed to exist between the independent variable *DMR* and the dependent variable μ, whereas the *RMR* is linearly related to the inverse of the total death rate i.e. $1/\mu$ (see Figure 4.1). The general form of the linear relationships in respect to the absolute and the proportional measure of the sex gap in mortality can be expressed as

$$DMR_i = A + B\mu_i + \varepsilon_i; \text{ with } i = 1, \dots, \text{n} \qquad (4.4)$$

and

$$RMR_i = A + B/\mu_i + \varepsilon_i; \text{ with } i = 1, \dots, \text{n}. \qquad (4.5)$$

Regression analyses are performed for Sweden, E&W and France for the time periods mentioned above, in each case separately for the young adult (18-39), middle adult (40-64), and old adult (65-89) population. Even though the HMD provides data up to 110+, age years 90+ were excluded from the study, since population counts rapidly decline, especially in historical populations. Observed patterns of the sex differentials at very old ages might be more due to statistical perturbations rather than being real effects. Homoscedasticity is tested for all regressions by using the Breusch-Pagan-Test (Breusch and Pagan 1979). In a pre-analysis, it was found that some regressions do not fulfill the criterion of

homoscedasticity, which means that the residuals are not evenly distributed. A reasonable explanation is that the DMR and the RMR experience unique changes within a time period, this being due to changes in sex-specific risk factors. Since the mortality rate declines over time, this would lead to heteroscedasticity. In order to evaluate the general association, homoscedasticity is not considered in the regression analysis.

Next, the association between the sex gap and mortality is analyzed in the age dimension. Since mortality rates and the DMR increase exponentially over adult age (see Chapter 3), a linear relationship can be assumed to exist between the logarithm of DMR and the logarithm of μ. Just as on the time dimension, the RMR is linearly associated with the inverse of the total death rates ($1/\mu$). DMRs, RMRs and μ are calculated for Sweden, France and E&W for single age years (18-89) and decade-wise (1870-9, 1880-9, …, 2000-9). The decade-wise counts of vitality data start at January 1st of the first year and end at December 31st of the last year of the respective decade.

A positive correlation coefficient (r-square) close to 1 (100% correlation), either on the time or age dimension, would imply an almost perfect correlation between the measure of the sex gap and the mortality regime. The correlation coefficient is divided into values smaller than 0.5 to reflect weak or no association, and they are gradually increasing from 0.5 to 1 in steps of 0.1 to evaluate the strength of an association. Secondly, a positive association implies a possible correlation of the DMR or the RMR with mortality rates, whereas a negative association does not. The exact slope of the RMR regressions are difficult to interpret, since they are related to the intercept and can only be analyzed relative to each other. In contrast, the DMR regression with a slope of 0.5 implies a proportional change of male compared to female mortality over time, since total mortality is approximately the mean between males and females. A slope bigger than 0.5 means that the DMR declines faster than expected with declining total mortality rates, whereas a slope smaller than 0.5 means delayed progress of the DMR compared to total mortality.

All calculations and figures were done using the statistical computing software R (version 3.01) and the integrated development environment software RStudio (version 0.97.551).

4.3 Results

4.3.1 Time Trend

Regression analyses show that both measures of the sex differential, the RMR and the DMR, are associated to mortality rates in most age groups and time periods in all three countries (Figures 4.3 and 4.4, Table 4.1). The correlations are, with some exceptions, mainly positive and significant (note, that a positive regression between the RMR and the inverse of mortality means an increase in the RMR with declining mortality rates). Moreover, the direction of the regression slope reveals some information about whether the numerical property can explain the change in the sex gap. A positive slope implies a possible relationship, whereas a negative slope implies that sex-specific risk factors counteract the numerical property. In Table 1, a yellow to red scale reflects the r-square values and therefore the strength of the relationship between the sex-differential and total mortality rates. The correlation strengths differ between both measures with the DMR being more strongly associated to time changes of mortality rates than the RMR for most of the analyzed periods. Two-thirds of the regressions concerning the DMR show a correlation coefficient of 80% or higher compared to one-third of the regressions when using the RMR.

General Trend 1872-2010

The DMR in E&W and France is highly correlated (70%) with the mortality regime in all age groups (r-squared > 0.7, Table 1). In Sweden the association is only weak for the old adult age group (25%), but high for young and middle adult age (98% and 87%). In contrast, the RMR is strongly associated to total mortality in all age groups in France (78-96%), whereas in Sweden and E&W the correlation coefficient is only strong at young adult age (84% and 94%), and slightly weaker for the other age groups (41-70%).

The slope of the correlation between the DMR and mortality throughout the complete time period is positive and relatively similar in all countries, around 0.5 or slightly lower. In the old age group, however, the slope is lower than 0.5 in all three countries. Concerning the RMR, the regression is also positive, meaning that the ratio increases with declining mortality rates throughout the past 128 years.

Pre-World War II Trend

The association strength between the RMR and the mortality regime is found to be above 50% in most countries and age groups (Table 1). It is lowest among young adult ages (12-55%) and highest among middle adult ages (67-84%). The RMR at old adult ages is not associated with mortality in Sweden and only moderately so in E&W (63%) and France (39%). In contrast, the change in mortality can explain the change in the DMR between 80% and 98% in Sweden and E&W, whereas in France the correlation is slightly weaker, ranging from 58% for old adults to 88% for the young population. No significant association between the DMR and mortality can be found for the middle age French population.

The slope of the DMR regression in the first time period is positive in all countries. In E&W the slope is around 0.5 except for the oldest age group, where it is slightly lower. Slopes higher than 0.5 are found in Sweden in the young and middle age group, and slopes lower than 0.5 are found at all ages in France. The RMR is positive for all age groups except for Sweden.

'Smoking Epidemic' Trend

After World War II, the so called smoking epidemic shows a rapid widening of the sex gap (Figure 4.2). During this time period, the RMR is strongly and positively related to the change in total mortality in France (76-91%) and Sweden (59-89%) in all age groups (Table 1). In E&W the correlation is strong for young adults (90%), weak at middle adult age (37%) and not significant among the oldest ages. Only in France, the DMR is positively associated with mortality in all age groups (r-squared: 57-89%). In Sweden and E&W the correlation coefficient is high for the young adults (95% and 84%), non-significant at middle ages and weak among the old ages (27% and 37%).

The regression slope of the RMR is positive in all countries and age groups, whereas for the DMR it is actually lower than 0.5 in all countries and even negative in the oldest age group in Sweden.

Post-'Smoking Epidemic' Trend

In the most recent time period analyzed the sex gap in life expectancy converges (Figure 4.2). This is reflected by the negative slope in the RMR versus mortality correlation in almost all countries and age groups (Table 1). The

exceptions are the oldest age group in France, which has a positive slope, and the young age groups in Sweden and E&W, which show no association between the RMR and mortality. The DMR is strongly associated with mortality in all countries and age groups, but especially at middle adult ages (100% correlation in all three countries).

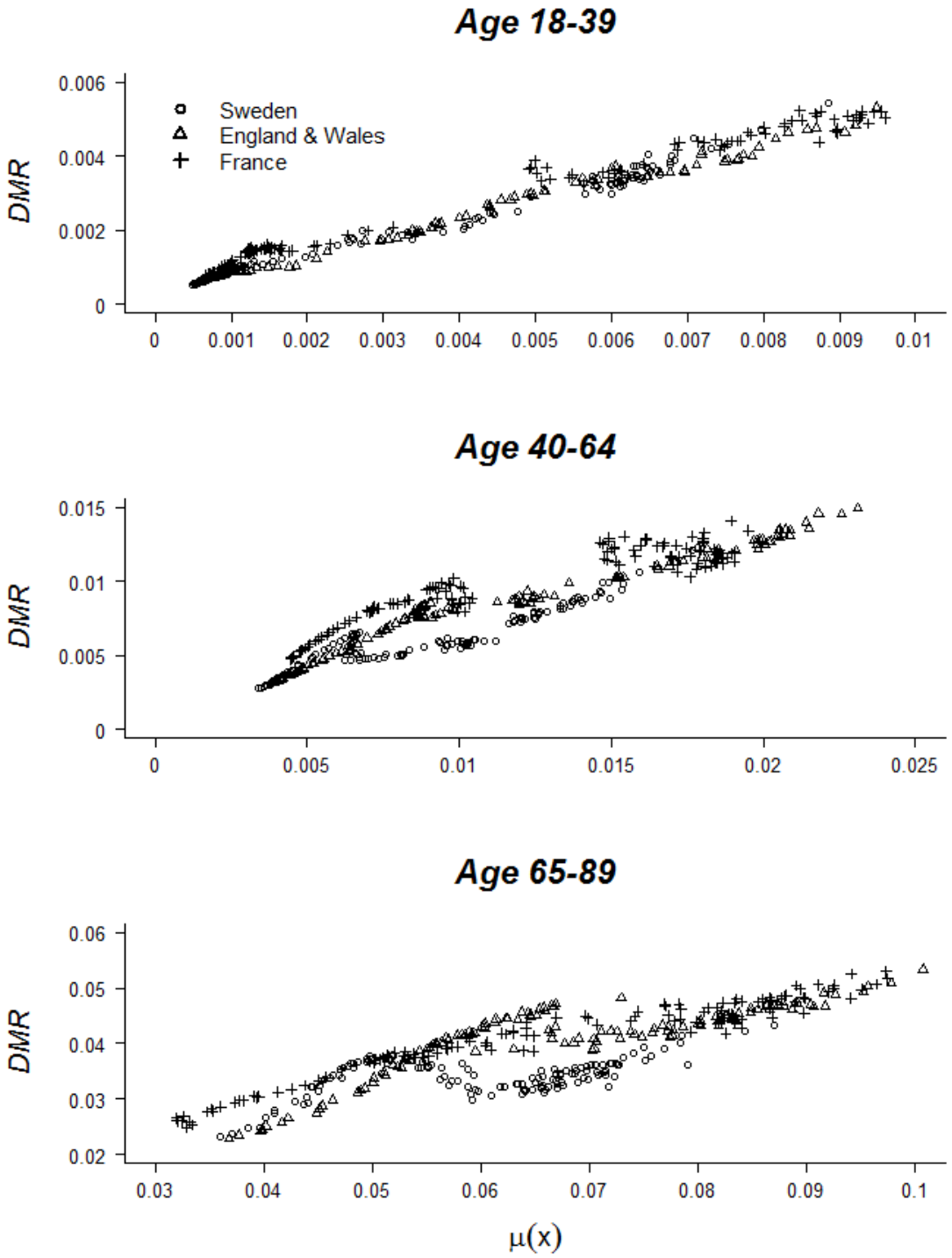

Figure 4.3. Difference between male and female mortality rates (y-axis) against age standardized mortality of the two sexes combined (x-axis) in the time period 1872-2010 (calendar years 1914-1920 excluded in all countries; 1939-1945 excluded in France and E&W).

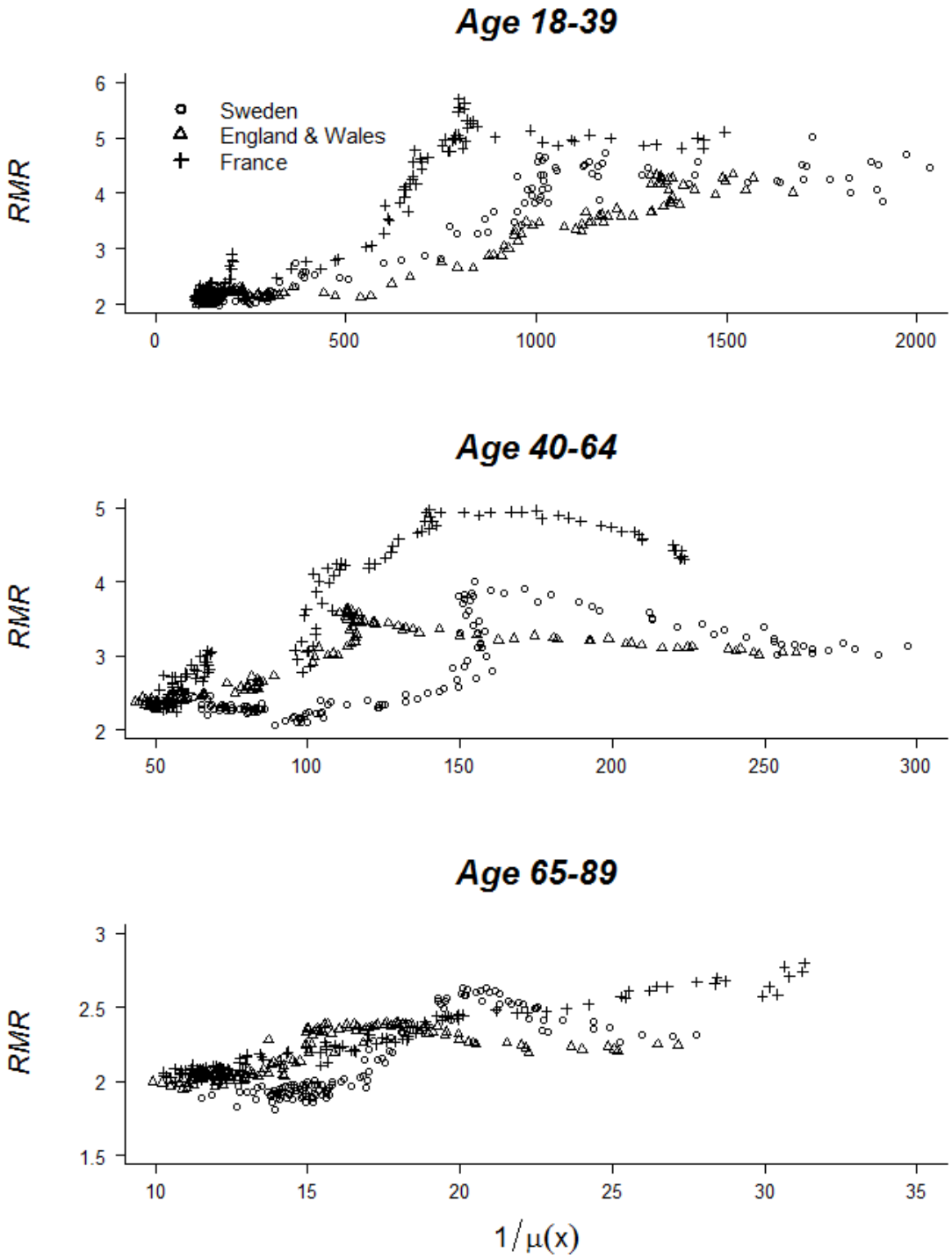

Figure 4.4. Ratio between male and female mortality rates (y-axis) against the inverse of age standardized mortality of the two sexes combined (x-axis) in the time period 1872-2010 (calendar years 1914-1920 excluded in all countries; 1939-1945 excluded in France and E&W).

Table 4.1. Sex differential versus mortality: Regression analyses for three selected countries for different age groups and periods (WW1 and WW2 excluded, see text for more information)

France, correlation DMR vs. mortality

Period Range	Age Group	slope	r-squared	p-value
1872-2010	18-39	0.48	0.98	<0.0001
	40-64	0.44	0.85	<0.0001
	65-89	0.35	0.93	<0.0001
1872-1938	18-39	0.4	0.88	<0.0001
	40-64	0.07	0.02	0.25
	65-89	0.33	0.58	<0.0001
1946-1992	18-39	0.29	0.78	<0.0001
	40-64	0.46	0.57	<0.0001
	65-89	0.41	0.89	<0.0001
1993-2010	18-39	1.25	0.99	<0.0001
	40-64	1.41	1	<0.0001
	65-89	0.63	0.91	<0.0001

England & Wales, correlation DMR vs. mortality

Period Range	Age Group	slope	r-squared	p-value
1872-2010	18-39	0.5	0.99	<0.0001
	40-64	0.53	0.95	<0.0001
	65-89	0.34	0.71	<0.0001
1872-1938	18-39	0.5	0.97	<0.0001
	40-64	0.53	0.98	<0.0001
	65-89	0.36	0.92	<0.0001
1946-1969	18-39	0.33	0.84	<0.0001
	40-64	0.15	0.03	0.44
	65-89	0.48	0.37	<0.01
1970-2010	18-39	0.54	0.6	<0.0001
	40-64	1.01	1	<0.0001
	65-89	0.94	0.99	<0.0001

Sweden, correlation DMR vs. mortality

Period Range	Age Group	slope	r-squared	p-value
1872-2010	18-39	0.49	0.98	<0.0001
	40-64	0.5	0.87	<0.0001
	65-89	0.15	0.25	<0.0001
1872-1931	18-39	0.64	0.93	<0.0001
	40-64	0.82	0.97	<0.0001
	65-89	0.49	0.8	<0.0001
1932-1979	18-39	0.4	0.95	<0.0001
	40-64	0.044	0.01	0.52
	65-89	-0.17	0.27	<0.001
1980-2010	18-39	1.07	0.98	<0.0001
	40-64	1.22	1	<0.0001
	65-89	1.14	0.97	<0.0001

France, correlation RMR vs. 1/mortality

Period Range	Age Group	slope	r-squared	p-value
1872-2010	18-39	0.003	0.83	<0.0001
	40-64	0.016	0.78	<0.0001
	65-89	0.036	0.96	<0.0001
1872-1938	18-39	0.004	0.55	<0.0001
	40-64	0.039	0.71	<0.0001
	65-89	0.033	0.39	<0.0001
1946-1992	18-39	0.006	0.91	<0.0001
	40-64	0.027	0.76	<0.0001
	65-89	0.042	0.86	<0.0001
1993-2010	18-39	-0.001	0.43	<0.01
	40-64	-0.012	0.92	<0.0001
	65-89	0.024	0.52	<0.001

England & Wales, correlation RMR vs. 1/mortality

Period Range	Age Group	slope	r-squared	p-value
1872-2010	18-39	0.0016	0.94	<0.0001
	40-64	0.005	0.41	<0.0001
	65-89	0.027	0.45	<0.0001
1872-1938	18-39	0.0006	0.25	<0.0001
	40-64	0.0073	0.84	<0.0001
	65-89	0.032	0.63	<0.0001
1946-1969	18-39	0.0022	0.9	<0.05
	40-64	0.03	0.37	<0.01
	65-89	0.019	0.06	0.24
1970-2010	18-39	0.0015	0.41	0.43
	40-64	-0.0032	0.93	<0.0001
	65-89	-0.02	0.76	<0.05

Sweden, correlation RMR vs. 1/mortality

Period Range	Age Group	slope	r-squared	p-value
1872-2010	18-39	0.0017	0.84	<0.0001
	40-64	0.006	0.48	<0.0001
	65-89	0.06	0.7	<0.0001
1872-1931	18-39	-0.001	0.12	<0.05
	40-64	-0.007	0.67	<0.0001
	65-89	0.01	0.05	0.09
1932-1979	18-39	0.0027	0.89	<0.0001
	40-64	0.022	0.59	<0.0001
	65-89	0.12	0.89	<0.0001
1980-2010	18-39	-0.0001	0.01	0.52
	40-64	-0.007	0.93	<0.0001
	65-89	-0.048	0.76	<0.0001

r-squared: r ≥ 0.9; r ≥ 0.8; r ≥ 0.7; r ≥ 0.6; r ≥ 0.5; r < 0.5; n.s.

DMR slope: slope < 0; 0 < slope < 0.45; 0.45 < slope < 0.55; 0.55 < slope < 0.95; slope ≥ 1

RMR slope: slope > 0; slope < 0; n.s.

4.3.2 Age Trend

Concerning the age dimension, the association between the DMR and the mortality regime is much stronger compared to that for the RMR (Figures 4.5 and 4.6). The mortality change over age explains between 70% and 95% of the age change in the DMR on a log-scale throughout all decades (Figures 4.7 and 4.8). In contrast, the RMR is only weakly associated with the mortality regime, explaining less than 50% for most decades. Moreover, the correlation is non-significant for the RMR for several decades between the 1870s and the 1950s (Sweden: 1870s-90s, 1910s-30s; E&W: 1950s; France: 1870s, 1890s, 1930s, 1950s), whereas it is only non-significant in one decade in respect to the DMR (E&W: 1880s).

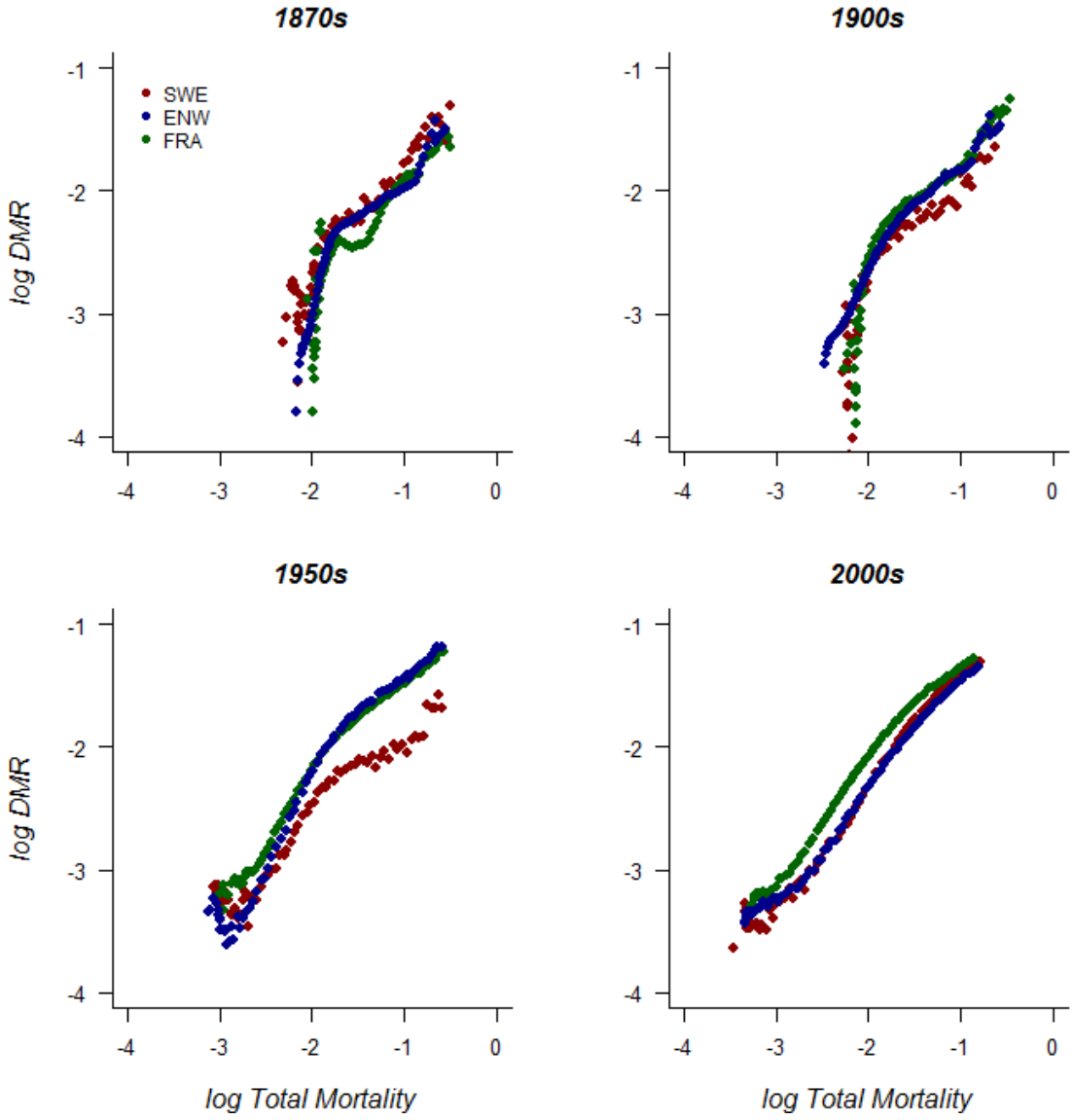

Figure 4.5. Logarithm of the difference between male and female mortality as a function of the logarithm of total mortality rates for single age years between 18 and 89.

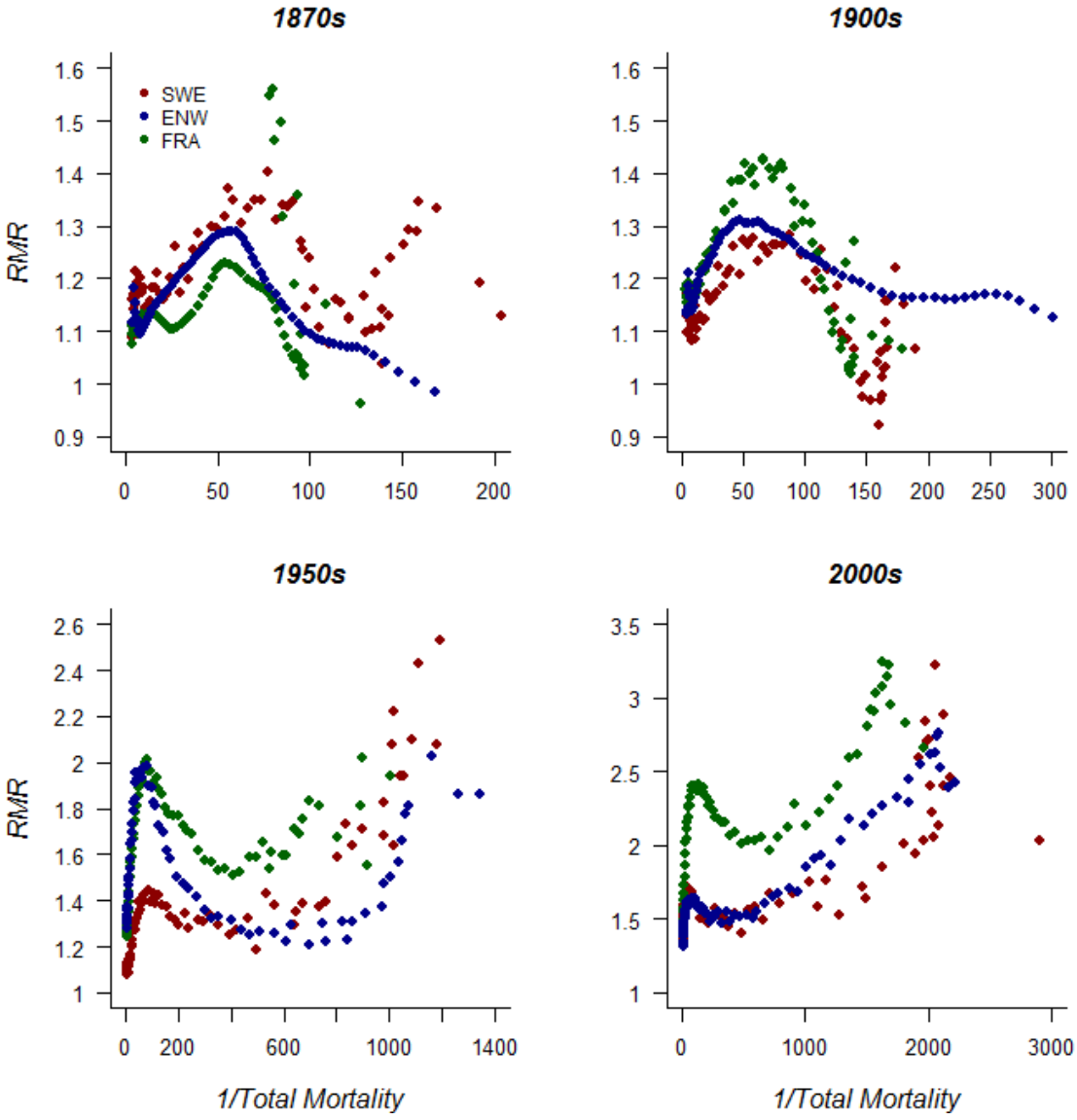

Figure 4.6: Ratio between male and female mortality as a function of 1/total mortality rates for single age years between 18 and 89.

Intercept

The intercept of the regression analysis between the log DMR and the log mortality rates increases between the nineteenth and the early twentieth century in E&W and France (Figure 4.7). After the 1910s it approaches a relative constant level compared to the previous decades in both countries. In the 1910s and 1940s the intercept moves slightly lower compared to the surrounding periods, likely due to both World Wars. In Sweden, the intercept declines until the 1940s, but increases afterwards, and is lower compared to other countries throughout the mid-twentieth century. Concerning the intercept, Sweden catches up with E&W and France in the

last decades of the twentieth century. Moreover, there is a reversal trend in the intercept in the last decades of the twentieth century in E&W and Sweden, but not in France.

In contrast to the DMR, the intercept of the regression for the RMR increases in all three countries from the 1870s until the end of the twentieth century (Figure 4.8). As with the DMR, there is a reversal of the intercept, which, however, starts earlier. France has the highest intercept in the second half of the twentieth century, whereas the intercept is lowest in Sweden during the mid-twentieth century. Moreover, E&W and France share the same intercept from the 1870s until the 1950s.

Slope

The DMR tends to increase faster than total mortality in the age dimension among all three countries until the 1930s. However, in the 1910s the slope declines likely due to WWI. After the 1930s, the slope parameter is below 1 in Sweden and E&W until the 2000s. In France, the DMR increases with the same pace as the mortality at adult ages in the decades from the 1940s to the 1980s. After the 1980s the slope declines to the same level as E&W and France.

The RMR tends to decline with increasing mortality rates (RMR increases with the inverse of mortality) until the 1930s in most decades, except for the 1910s. With the beginning of the second half of the twentieth century, the slope becomes positive.

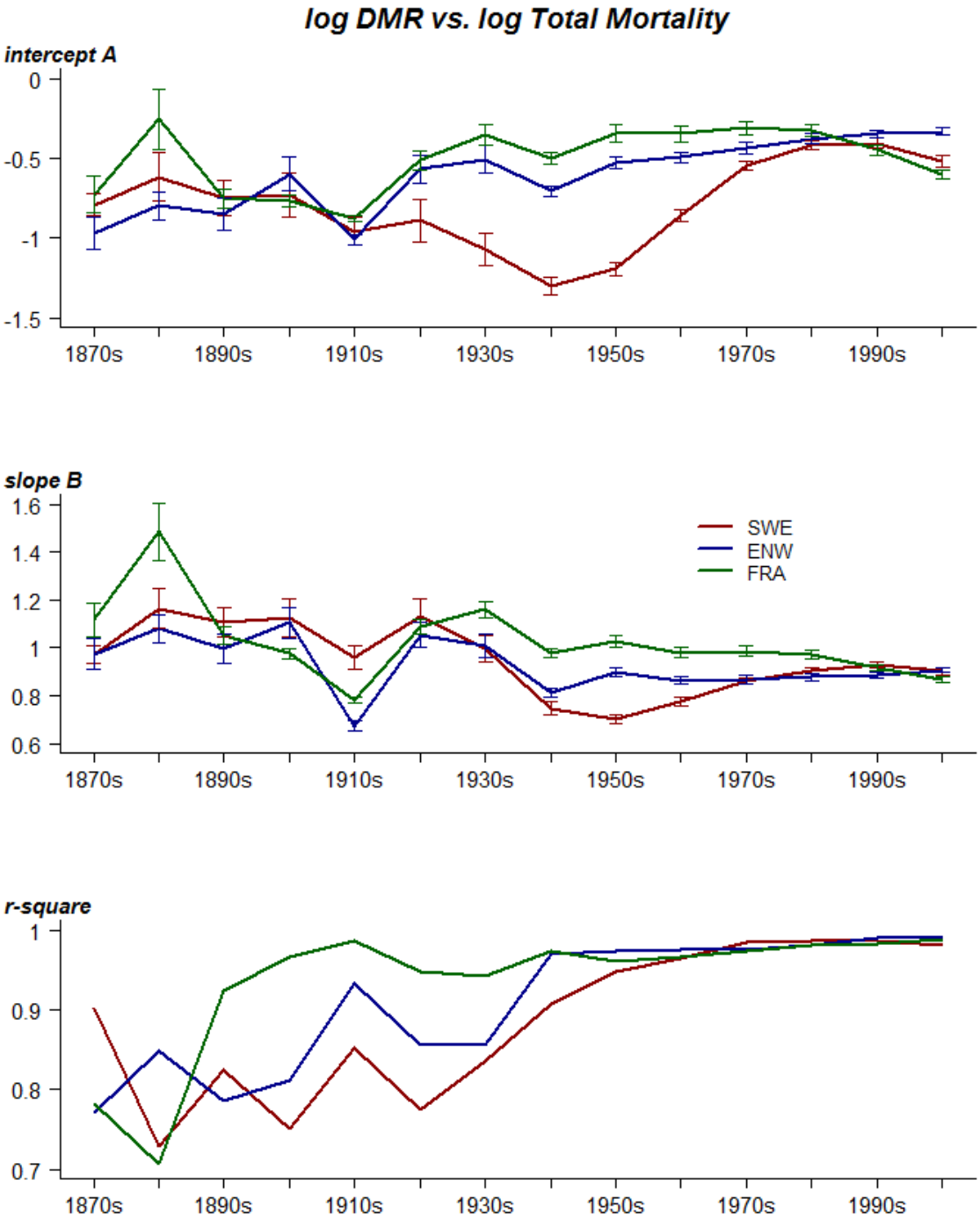

Figure 4.7. Intercept, slope and correlation coefficient of the regression analysis decade-wise from the 1870s to 2000s: Difference between male and female mortality versus total mortality rates between ages 18 and 89.

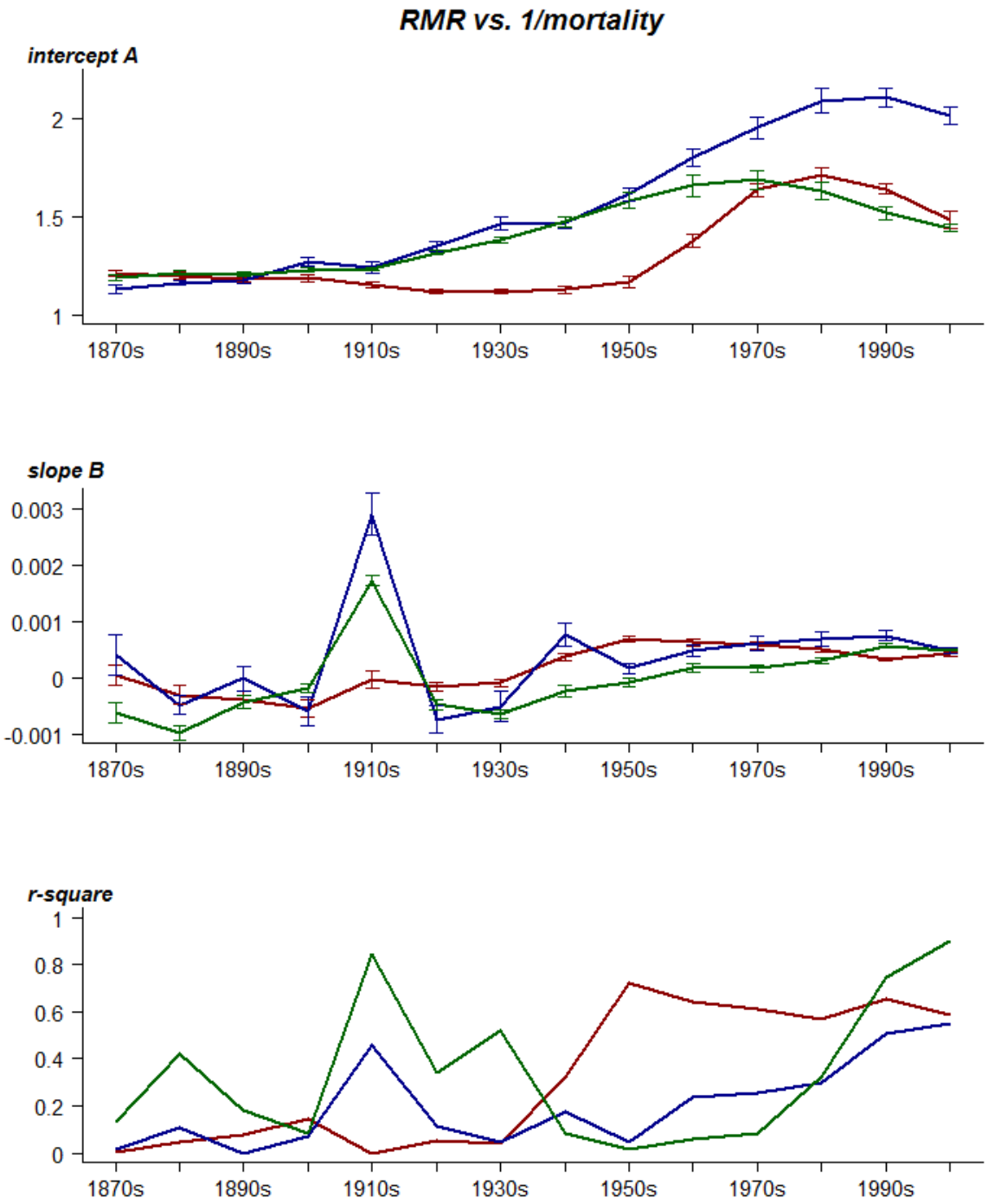

Figure 4.8. Intercept, slope and correlation coefficient of the regression analysis decade-wise from the 1870s to 2000s: Ratio between male and female mortality versus mortality rates between ages 18 and 89.

4.4 Discussion

This study examined to what extent the relative (RMR) and the absolute (DMR) sex differential in mortality is related to the mortality regime in a historical context. Two dimensions were examined: The time dimension is characterized by a decline of total mortality rates. The sex gap by means of the ratio widens for all age groups throughout the twentieth century, whereas the DMR tends to decline at young ages but increases at old ages (see Chapter 3). In the present chapter, it was examined to what extent the historical trends of both measures might be affected by their numerical properties. Since different age groups are affected by different risk factors, the analysis was performed separately for the young, middle and old adult age groups. In summary, the aim was to estimate the influence of the mortality regime on the sex differential to evaluate the significance of the absolute and relative measures as an approximation of real underlying sex differentials in risk factors. Secondly, a similar problem as on the time dimension exists in the age dimension, since mortality rates as well as the DMR increase over age, whereas the RMR tends to decline.

The analysis of the time dimension revealed that both measures, the DMR and the RMR, are correlated with the mortality regime. Nevertheless, the RMR is less affected by changes in mortality rates compared to the DMR (Table 4.1, Figures 4.3 and 4.4) and, hence, provides a better picture of the evolution of underlying sex-specific risk factors. An explanation for this finding is that sex-specific risk factors may affect mortality in proportional, rather than in absolute terms.

However, for some age groups and time periods the RMR is also strongly correlated with declining mortality rates. For example, during the ‘smoking epidemic’ the RMR in the young age group is driven up to 90% by changes in mortality across all countries (Table 1). Hence, a large part of the ‘young male syndrome’ observed in the second half of the twentieth century may be due to the numerical issue. An explanation for this finding might be that the steep increase after World War II of the ratio in male to female mortality in young adults in westernized countries might stem from a decline in sex-unspecific rather than from sex-specific risk factors. The high correlation coefficient between the DMR and total mortality confirms this statement. Since both measures are highly correlated with the

mortality regime, it is likely that the change in the sex gap is mainly driven by a decline of sex-unspecific risk factors.

4.4.1 'Smoking Epidemic'

During the 'smoking epidemic' the sex gap by means of the ratio also correlates with mortality in the middle and old age groups in France and Sweden, but slightly weaker compared to young adult ages (Table 1). In contrast, a lack of the correlation between age 40 and 89 in E&W implies a stronger effect of sex-specific risk factors driving the relative and absolute sex differential. Actually, coronary heart diseases (CHD), which increased especially in middle to old adult aged males throughout the twentieth century (Lowler et al. 2001), are a leading force of the diverging sex gap in life expectancy (e.g. Lopez & Ruzicka 1983). A possible explanation for the negative association between the RMR and mortality as well as the high slope found for the regressions of the DMR between ages 40 and 89 (Table 1) is that CHD drives the proportional sex gap in mortality and amplifies the effects of the numerical property. Support for this assumption is that in France the absolute difference in CHD is much lower in the second half of the twentieth century (Lowler et al. 2001), although the correlation between the RMR and mortality is much stronger compared to E&W (Table 1). Hence, the change in sex-specific risk factors is relatively low compared to sex-unspecific risk factors in France, leading to a higher correlation coefficient of the regression between mortality rates and the RMR and DMR, respectively. However, Sweden shows a higher correlation coefficient, even though the sex difference in CHD was comparably high during the twentieth century to that in E&W (Lawlor et al. 2001). Nevertheless, the sex gap in life expectancy in Sweden is much lower compared to E&W and France. Hence, CHD only explains parts of the change of the sex gap by means of the RMR during the 'smoking epidemic'. Another remarkable finding concerning the 'smoking epidemic' is that the DMR is weakly correlated with mortality for Swedish and E&W individuals of middle and old age and, hence, appears to be more meaningful in reflecting changes in sex-specific risk factors than the RMR for these age groups.

4.4.2 Post-'Smoking Epidemic'

The converging trend in the RMR in the last decades, the post-'smoking epidemic', is apparently not a consequence of the numerical issue. The correlations are negative in most cases, meaning that the RMR declines, even though the mortality rate declines, too (Table 1). In contrast, the DMR is highly correlated with mortality rates. At first glance, this implies weak explanatory strength for the DMR. However, the slope of the association is >1, which means that the DMR declines faster than mortality rates. Hence, it can be concluded that a change in sex-specific risk factors is the main driver for the RMR and the DMR and explains the reversal trend of the converging sex gap. Moreover, if the RMR declines with declining mortality rates, the association between the DMR and mortality can be expected to be high and > 0.5. Therefore, a comparison of the DMR and the RMR may help to identify, whether a real time trend of sex-specific risk factors exists. This was actually the case for the historically converging trend of the RMR in Sweden between 1872 and 1931. These changes can be attributed to real changes in sex-specific risk factors, since the correlation between the RMR and 1/mortality is negative. The reduction in excess alcohol consumption in the Scandinavian male population between the nineteenth and twentieth may explain this trend (Fridlizius 1988).

4.4.3 Age Pattern

The age pattern of the RMR seems to be less affected by sex-unspecific risk factors compared to the DMR (Figures 4.7 and 4.8). Moreover, the negative relationships between RMR and mortality rates until the early twentieth century indicate that sex-specific risk factors accounted for a reversal of the numerical trend. In recent decades, however, low mortality rates at young ages (equal to high values of the inverse of mortality) are related to a high RMR, reflected by a positive slope. Hence, the RMR tends to decline over age due to the numerical issue. However, the 'hump' of the ratio around age 60, which is typical for modern western populations (Lopez 1983), is clearly driven by sex-specific risk factors. At the end of the twentieth century and with the beginning of the twenty-first century, the age pattern

of the RMR is strongly affected by the numerical property, which explains between 50% and 90% of the association.

A remarkable finding of this study is that the logarithm of the DMR increases almost linearly with the logarithm of mortality rates throughout the second half of the twentieth century (Figure 4.5), whereas the RMR is characterized by a non-linear trend (Figure 4.6). The trend in the DMR is therefore predominantly driven by a change in sex-unspecific risk factors. However, it seems that developed countries approach a level, for which the age pattern of the DMR is fixed, but still present. The slope of the relationship between the DMR and mortality converges to a certain level in all countries. The intercept of the correlation drives the decline in the DMR in the more recent decades. This leads to the conclusion that extrinsic risk factors exacerbate a biological fixed limit of the sex gap leading to a converging trend. This finding offers an opportunity to distinguish extrinsic mortality from mortality, which stems from the interaction of extrinsic and intrinsic risk factors. This is, however, beyond the scope of the current study and calls for further research.

4.5 Conclusions

- Changes of the RMR or DMR do not necessarily reflect relative or absolute changes in sex-specific risk factors. Their interpretational strength is context-specific and depends on the age group and time period of interest.
- The widening of the relative sex gap in mortality after World War II at young ages is likely due to a rapid drop in mortality rates in both sexes and therefore predominantly driven by sex-unspecific risk factors. For other age groups, however, the RMR, but also the DMR, may be capable of reflecting sex-specific risk factors.
- In general, a proportional measure of the sex differential in mortality has more explanatory strength than an absolute measure. However, changes in the RMR do not fully reflect changes in sex-specific risk factors. The association is context-specific, and both measures should be considered in analyses of the sex gap. Moreover, more attention should be devoted to the relative contribution of sex-specific and sex-unspecific risk factors to the sex gap.

Part II

Middle Mortality

Chapter 5

Theoretical Concept of a Mortality Model based on Interaction of Internal and External Risk Factors

Questions about the pace of living and dying have fascinated people since time immemorial. The great Greek philosopher Aristotle compared in his text *On youth and old age, on life and death, on breathing* the pace of living to a burning fire. According to his metaphor, the fire may be put out by extinction or exhaustion. Where the latter is the natural way of dying, Aristotle understood the former to be a violent death. The important point of Aristotle's definition is the clear distinction between these two principal processes of dying, which have shaped people's thoughts about death to the present day. In the nineteenth century, Aristotle's idea was applied to population dynamics. The well-known demographer Wilhelm Lexis speculated in 1877 about the statistical consequences of these two mechanisms leading to the dying out of a generation. He used the analogy of a ball throwing game. In Lexis' mind game the thrower tries to throw the balls, each of them representing an individual, exactly 70 feet away. The distribution around the 70 foot mark reflects the statistical distribution of individuals who died from a natural or *senescent* death around age 70. Only a few individuals were fortunate enough to reach that old age at the time Lexis lived. Several died as infants or children. Lexis compared them with balls, which are in bad shape and too heavy to throw. The thrower just drops them in front of himself. Between 15 to 40 feet away from the thrower, another person tries to catch the balls and puts them on the ground at the position where he catches them. The distribution of the balls between the 15 and 40 foot marks reflects *anticipated*, also called *premature*, deaths. According to Lexis and Aristotle (and, of course, many others) the duration of life is restricted to the intensity of *anticipated* deaths, but people could live the biologically maximum lifespan, if the catcher in Lexis' analogy could be taken out or if the fire is not extinguished from the outside, as Aristotle argued.

Inspired by this basic idea, demographers in the nineteenth century, notably Benjamin Gompertz (1825), began to develop the so called *law of mortality*, $\mu(x)=ae^{bx}$. This simple model contains two parameters, a and b, and provides a good

approximation of human mortality as a function of age after maturity, $\mu(x)$. Moreover, the exponential increase of adult age mortality is a universal property of human populations and a biological characteristic of human aging (Sas et al. 2012). The *law of mortality* is a parsimonious solution as it provides the most explanatory strength with the fewest parameters. For these reasons, the model became an important tool to estimate physiological aging in humans and a variety of other species in the last 100 years. However, mortality at young adult ages is higher than it would be expected to be from the Gompertz *law*. To account for this deviation, William Makeham (1860) added a constant term to the Gompertz *law*, so that $\mu(x)=ae^{bx} + c$. Parameter *c* refers to extrinsic, background, anticipated or premature mortality. The interpretation is that extrinsic mortality is decoupled from intrinsic mortality by a simple partition.

However, the concept of a distinction between extrinsic and intrinsic mortality is misleading. Mortality is rather a function of the intrinsic constitution of an individual and his/her exposure to extrinsic risk factors. In other words, mortality risk means that the individual is not capable of withstanding an extrinsic stressor. Intrinsic capability declines over age due to the biological process of senescence. The Gompertz *law* can be interpreted in this way. The interaction of a constant external stressor, denoted by the intercept parameter *a*, leads to an exponential increase due to the age specific loss in physiological function, denoted by *b*. Makeham's parameter *c* is, however, decoupled from the interaction of extrinsic and intrinsic risk factors. William Makeham himself knew about the interpretational weakness of *c* and noted that mortality is caused by "*disease depending for their intensity solely upon the gradual diminution of the vital power, and those which depend upon other causes, the nature of which we do not at present understand"* (Makeham 1867, p. 335). Hence, he doubted that a simple constant term reflects a real mechanism leading to deaths at young ages, but he was aware that the partition of mortality provides a better estimation of human mortality. Even though Makeham's term had practical purposes, little attempt has been made to incorporate *other causes* into mortality modeling. Such other causes may be driven by extrinsic risk factors. For example, behavioral, social and environmental risk factors may vary over age. Hence, a more realistic mortality model should incorporate the interaction

between varying extrinsic and intrinsic risk factors instead of assuming mortality to be either explicitly intrinsic or extrinsic.

At first glance, it seems difficult or even impossible to disentangle extrinsic from intrinsic risk factors. However, it would be feasible to formulate a mortality model with an approximate idea of the age pattern of extrinsic risk factors. Actually, several findings in demographic, psychological and epidemiologic research indicate that extrinsic risk factors follow a certain age trajectory. This auxiliary information serves as a framework in building up an *explanatory* model of mortality. In contrast to *explanatory* models, *descriptive* models usually do not provide a deeper mechanistic explanation of its parameters, but are developed to improve the fit of mortality curves. Such models have been extensively developed by actuaries in the past, but they fail to allow for a deeper interpretation. Below, an *explanatory* approach is used to develop a simple two component mortality model.

5.1 Explanatory and Descriptive Models of Mortality

Explanatory models are based on background knowledge of biological (intrinsic) or environmental (extrinsic) risk factors to justify a given age-dependent trajectory of mortality rates. The Gompertz *law of mortality* occupies a central role in both modeling approaches. It was originally developed as a *descriptive* model with a good fit to human data. Since it expresses mortality as an exponential function over age, it has been strongly suggested to capture the link between biological aging and death (Sas et al. 2012). Due to these properties, Gompertz's *law of mortality* eventually became the most popular model in (bio-) demographic and (bio-) gerontologic research. However, two important points weaken its explanatory strength. First, even though mathematical models attempt to connect the molecular process of aging to the exponential increase in mortality, the physiological mechanisms of aging are still a black box. Secondly, extrinsic risk factors affect the slope parameter b of the Gompertz *law* and weaken its connection to biological senescence. Whereas the biological meaning of the exponential age pattern of mortality is commonly accepted due to stunning empirical data, less is known about the age pattern of extrinsic mortality. Even though Makeham's extension of Gompertz' *law* by an extrinsic component accounts for this problem, it is only a

descriptive solution with limited *explanatory* strength. This is mainly, because the extrinsic component is masked by the Gompertz component at old age and obscures the real pattern.

In spite of these difficulties, the potential gain of finding a meaningful mortality model would be enormous. It could provide deeper insights into the rate of physiological aging and the contribution of extrinsic risk factors to mortality between the sexes and other subpopulation in humans or other species. For example, the reduction in extrinsic risk factors mainly accounts for the improvements in total adult mortality observed throughout the last 150 years in Westernized countries (Bongaards 2005).

The use of mortality models for estimating extrinsic risk factors in a population has many advantages compared to other methods. Mortality data are available for a huge variety of contemporary as well as historical populations. For example, causes of death (COD) data might be a possible source for disentangling extrinsic and intrinsic mortality patterns. It is also available for a broad range of contemporary and historical populations, but is characterized by high uncertainty. Especially at old ages, death certificates become unreliable (e.g. Modelmog 1992). Furthermore, COD data is often one-dimensional and does not take the interaction of extrinsic and intrinsic risk factors into account. Moreover, the identification of different diseases has improved and classifications have changed over time, which requires an adjustment of older COD tables. Due to these problems, a parametric model of total mortality is an elegant solution to assess the contributions of extrinsic and intrinsic risk factors. In order to formulate a new concept and a reasonable expression of the extrinsic mortality component, this work aims to

- briefly discuss the biological implications of the Gompertz *law*,
- discuss the most important attempts to express the extrinsic mortality component,
- provide evidence for an age-dependent non-Gompertz mortality component and
- provide an alternative approach to interacting intrinsic and extrinsic risk factors.

5.2 The Gompertz Law and its Biological Implications: A brief Outline

One of the first attempts to find a mathematical expression for the relationship between age and mortality traces back to Abraham de Moivre (1725), who stated that in a population the force of mortality can be expressed as

$$\mu(x) = \frac{1}{\omega - x} \qquad (5.1)$$

with μ being the force of mortality at age *x and* ω representing the age at which the mortality rate becomes infinite (de Moivre set ω to 86). The model has been developed to describe adult mortality, but fits poorly, especially for contemporary populations (see Figure 5.1).

A century later, Benjamin Gompertz (1825) provided a more promising approach. He first discovered that the steady rise in the chance of dying doubles at certain intervals (approximately every 8 years). He discovered that the death rate follows a geometrical function, which can be expressed as

$$\mu(x) = ae^{bx} \qquad (5.2)$$

with *a* denoting mortality at the initial age (Gompertz set it to 30). The virtues of Gompertz' *law of mortality* compared to former *laws* is that it accurately fits not only a huge variety of human, but also animal data (Finch 1990). Therefore, its slope parameter *b* reflects an underlying biological process of aging by (e.g. Economos 1982). Gompertz himself speculated about the biological implications of the geometrical progress in mortality. He noted that "*death may be the consequence of two generally coexisting causes; the one, chance, without previous disposition to death or deterioration; the other, an unspecified force that destroyed the material of organization necessary for life*" (Gompertz 1825, p.517). To express this in another way, Gompertz distinguished external causes of death, independent of the vitality of an individual, from an internal aging process. Although Gompertz was not aware of proximate modern theories of physiological aging, he vaguely mentioned that there must somehow be a kind of depletion on the micro-level of an organism. Some decades later, in 1867, William Makeham noted that "*some diseases depend[] for their intensity solely upon the gradual diminution of the vital power*" (p.335). Gompertz's slope parameter *b* provides information on how mortality rates

accelerate over age and is therefore an approximation of *the rate of aging* (*ROA*). The *ROA* is defined as the relative derivative of the *force of mortality*,

$$ROA = \frac{dln[\mu(x)]}{dx} \qquad (5.3)$$

The *ROA* can be interpreted as the indirect consequence of physiological aging processes among individuals in a given population. It is comparable to compound interest. Unlike the economic form of debt, though, cell damage cannot be paid off. A population pays only the compound interest for life in terms of an increasing mortality risk. A basic level of cell damage is inherent to each individual at birth. As the cell damage increases over age, this causes more damage to other cells or components. This leads not only to damage accumulation, but also to its acceleration over age. As he/she grows older, the individual pays the price with increasing frailty and a higher susceptibility to external stressors. Even though the Gompertz *law* somehow reflects the micro-level of senescence, there is no persuasive proof yet. However, there are many mathematical attempts to incorporate physiological functioning and the mortality pattern. A historical background of these attempts is provided in the following sections.

5.2.1 Senescence and Gompertz Law of Mortality

Since the exponential behavior of adult mortality can also be found in the kinetics of enzymatic reactions, biologists in the early twentieth century started to connect chemical processes to the accelerated dying out process of populations (e.g. Loeb & Nortrop 1916, 1917, Brody 1924). However, a broadly accepted mathematical theory which connects the *rate of aging* to a biological process has not yet been formulated (Olshansky and Carnes 1997).

A first interpretation of the biological meaning behind the exponential increase in mortality rates was provided by Benjamin Gompertz, who noted that death is due to "*a deterioration, or an increased inability to withstand destruction*" (Gompertz 1825, p. 517). With his concept, Gompertz was the first who inaugurated the search for a biological justification of his *law of mortality* (Olshansky and Carnes 1997). In the nineteenth century nearly nothing was known about the underlying biological mechanisms leading to a decline in physiological and organ functions. William

Makeham highlighted this fact by noting in his renowned article "On the Law of Mortality": "*I do not profess to separate the whole category of diseases into the two classes specified—viz., disease depending for their intensity solely upon the gradual diminution of the vital power, and those which depend upon other causes, the nature of which we do not at present understand. I apprehend that medical science is not sufficiently advanced to render such a desideratum possible of attainment at present"* (Makeham 1867, p. 335).

Makeham was also the first who mathematically distinguished two different mechanisms leading to death: senescence and non-senescence (all kind of deaths, which are not "*depending for their intensity solely upon the gradual diminution of the vital power*"). Whereas William Makeham and Benjamin Gompertz had philosophized about unspecified intrinsic forces, researchers in the early twentieth century started to explain these forces with comparison to the nature of chemical reactions (Olshansky and Carnes 1997).

Two of the theorists of this new research field were Jaques Loeb and John Howard Northrop. They started temperature experiments on different strains of *Drosophila* and found that the lifespan approximately doubled with every 10 C° of temperature decline (Loeb and Northrop 1916, 1917a, 1917b). Based on their findings, Loeb and Northrop argued that the "*duration of life were limited by the cumulative injurious effects of certain products of metabolism*" (Loeb and Northrop 1916, p. 456). This concept was surprisingly foresighted and was later rephrased in the *rate of living* theory by Raymond Pearl (1928). It again was expanded by the *radical theory of aging*; an explanatory framework about the molecular agents mediating the damage accumulation in the cell (Harman 1956, 1992). Furthermore, Loeb and Northrop (1916) suggested that the temperature positively affects some immeasurable cumulative injuries and reduces life span in *Drosophila*. However, the connection between a chemical law and the rate of aging was no more than a theoretical passage and was not transformed into a mathematical expression.

This step was the first subject of Samuel Brody's article "The Kinetics of Senescence" (1924). He formulated the bio-molecular mathematics of mortality and stated that he found a simple negative exponential function to describe several measures of vitality decline (Brody defined vitality as the reverse of senescence). He further noted that mortality increases in the same proportion as vitality declines and

argued that this might be a biological law, since "*this exponential law is the same as the law of monomolecular change in chemistry*" (Brody 1924, p. 257). However, later studies showed that the functional ability of various body systems, for example, maximum nerve conduction velocity, vital capacity and maximum breathing capacity, decline approximately linearly with age (e.g. Brandfonbrener et al. 1955, Norris et al. 1953, Shock & Yiengst 1955).

5.2.2 Senescence: A Universal Property of the Life Table?

Because of the limitation of quantifying the chemical reactions in the cell, the interest shifted to a search for a universal property of the life table, which was assumed to be determined by the damage processes on a molecular basis (Brownlee 1919). Based on this idea, an ambitious project was brought into being by Raymond Pearl and colleagues (Pearl and Parker 1921). Their intention was to bring out a paper series in which they present the progress in developing such a universal measure, which is suitable to compare the determinants of senescence among different populations and species. Raymond Pearl became the leading scientist in the discipline of bio-gerontology and led the intellectual discussion of this topic for more than a decade. A main problem of life table comparison was the lack of standardized life spans for different species; e.g. *Drosophila* life span is measured in days, but that of humans in years. Pearl subdivided the age range into percentiles for different species and then compared demographic properties based on these standardized life spans. He revealed a surprising similarity in the survival function, e.g. between *Drosophila* and humans (Pearl 1922), but failed in making significant progress beyond this finding. Further, the description of survival and mortality curves were purely qualitative, whereas a quantitative property remained unspecified. After more than one decade and 14 editions of the article series "Experimental studies in the duration of life", Raymond Pearl and John Miner stated that it is "[not] possible … to present a rational and complete theory of natural death and its distributions relative to time (age)" (Pearl and Miner 1935, p. 74).

The authors justified their decision to stop searching for a biological law for life tables with the argument that too many endogenous and exogenous factors play a role in the death of an organism and that these factors are not detectable within the available data. They suggested postponing the search to a time when a qualitatively

higher level of data collection was attainable (Pearl and Miner 1935). However, with their sobering declaration, the search for a biological law of mortality ended for the time being (Carnes et al. 1996). Major Greenwood and Joseph Irwin stated that these early attempts by Raymond Pearl were characterized by a "*theorizing [that] was only an agreeable intellectual amusement*" (1939, p.2). Nevertheless, the contribution of Raymond Pearl and colleagues motivated subsequent bio-gerontologists to approach the problem from a different perspective. Two decades after Pearl and Miner's chastening statement, new promising theories of the biochemical, physiological, stochastical and evolutionary process of senescence were formulated to allow for a better understanding and a more differentiated contemplation of the biological mechanisms.

5.2.3 Mathematical Justification of the Gompertz Law

Bernhard Strehler and Albert Milvan (1960) used the findings of a steady decline in physiological function to formulate a mathematical relationship to the exponential pattern of mortality. While the vitality of an organism is steadily diminishing over age, it is also subject to frequently repeating external challenges. If these challenges exceed the remaining vitality, death occurs. Strehler and Mildvan proposed that the probability of the intensity of a shock is expressed in the Maxwell-Boltzmann distribution (1960), which describes the distribution of energy among molecules in a gas at a given temperature. The Maxwell-Boltzmann equation describes an approximately negative exponential curve. Strehler and Milvan (1960) argued that on the left side of the distribution the frequency is the highest for very small shocks, like a cut finger, whereas on the right side, the shocks with the smallest probability have the highest impact on vitality, such as severe car accidents or serious infections. The resulting distribution of deaths over age follows a Gompertz function. However, the exponential function of mortality derives directly from the assumption of the Maxwell-Boltzman equation. Moreover, the Strehler-Mildvan model of mortality was not only criticized for circular reasoning, but also for being too simplistic (Yashin et al. 2000). Follow-up models included stochastic processes (Sacher and Trucco 1962), homeostasis (Economos 1982) or heterogenous populations (Vaupel et al. 1979) to develop more sophisticated approaches to mortality dynamics (for a discussion see Yashin et al. 2000).

5.3 Extrinsic Mortality

One main reason for this failure to explain the demographic property of aging is that the *ROA* is not entirely connected to the biological process of senescence. Adult human mortality usually shows some deviance from a perfect exponential curve. It was suggested that such perturbations were due to external causes, which Aristotle referred to as violent death, rather than to changes in intrinsic aging processes (e.g. Hallén 2009). It was William Makeham (1867) who first assumed an extrinsic mortality component and extended Gompertz' *law* by adding a constant *c* to it:

$$\mu(x) = ae^{bx} + c \qquad (5.4)$$

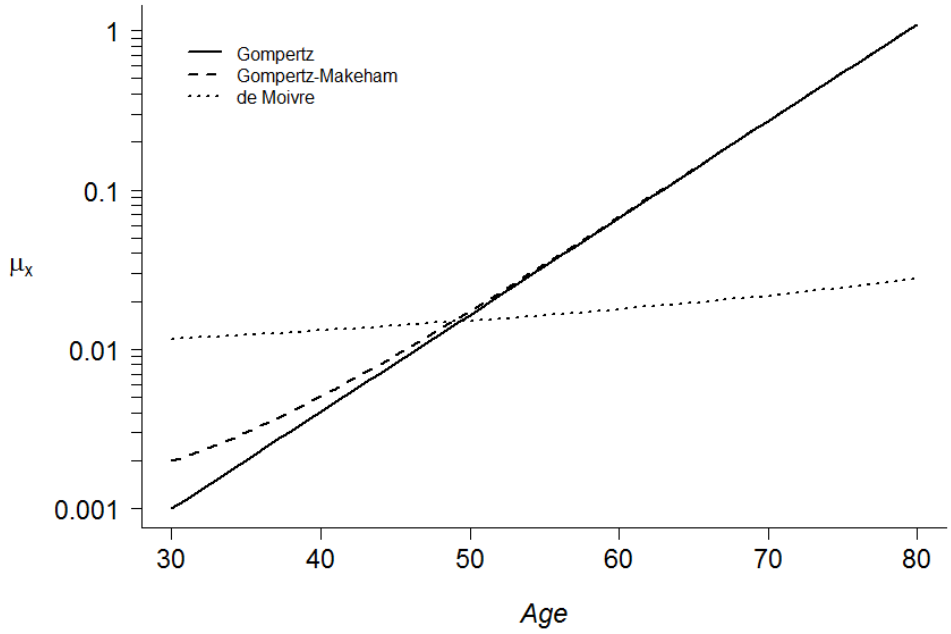

Figure 5.1. Different mortality models according to Abraham de Moivre, Benjamin Gompertz and William Makeham (a=0.001, b=0.14, c=0.001, ω=86). See text for more information.

For Makeham, Gompertz's *law of mortality* represents the biological age-dependent, or *senescent*, component, whereas the constant *c* reflects *non-senescence*. Makeham himself was aware that *senescent* and *non-senescent* causes compete for

lives, but was unable to disentangle them in his time. Hence, in respect to the *Gompertz-Makeham law*, the *ROA* does not reflect only senescent mortality, but also a constant component reflecting extrinsic mortality. Therefore, extrinsic mortality lowers the *ROA* (e.g. Gavrilov and Gavrilova 1991, Hallén 2009). In the Gompertz model, parameter *b* alone reflects the *ROA*, whereas in Makeham's extension, which corrects for extrinsic mortality, parameter *b* is not equal to the *ROA* anymore, but to some quantity that may be called the *rate of senescence* (*ROS*). The *ROS* can be defined as the acceleration of mortality over age due to vitality decay without any influence of extrinsic risk factors.

Hence, the *ROS* reflects the intrinsic process of damage accumulation, whereas the *ROA* is the demographic rate of aging. However, mortality due to extrinsic risk factors is difficult or even impossible to distinguish from mortality due to physiological aging. This is because deaths often occur from the interaction of both. Thus the *ROS* cannot be directly estimated. A method is to partition mortality and approximate intrinsic and extrinsic mortality components by defining a simple mathematical solution.

An important contribution of William Makeham in the field of demography was the idea of partitioning mortality into several components. Even though Makeham's primary motivation was to provide a descriptive solution to improve the fit of Gompertz's model, it also had many implications for the nature of deaths. Most models so far have been developed by actuaries to calculate insurance costs or forecast mortality trends in the future (e.g. Wetterstrand 1981). Therefore, the extrinsic component of mortality has often been purely descriptive without parallels to the real mechanisms. Especially the mortality hump at young ages has been used as an anchor point to construct models that fit best. Thorwald N. Thiele, for instance, used an exponential quadratic function for the hump (Thiele & Sprague 1871). The component increases fast from maturity and peaks between age 20 and 30. After the climax, the curve rapidly declines and becomes negligibly small at older ages when the Gompertz term dominates. Also more recent models assume a rapidly declining term for middle adult age mortality similar to Thiele's model (e.g. Heligman & Pollard 1980). However, the non-Gompertz component may be relevant even at older ages. The following sections list evidence for this hypothesis based on studies

and on own preliminary findings. In order to account for the importance of the non-Gompertz component at middle adult ages, it is called here *middle-aged mortality*.

5.3.1 The Age Pattern of Middle Mortality

In order to assess the age pattern of *middle mortality*, several studies are presented. In general, it is commonly accepted, that the Makeham term reflects the non-Gompertz component and has often been interpreted as extrinsic mortality caused by accidents, violence and infectious diseases (e.g. Bongaarts 2006, Hallén 2009). There are other expressions such as that from Thiele (1871) or Heligman and Pollard (1980) which presume a negligibly small non-Gompertz component at older ages. Nevertheless, a few studies have found that the age pattern of extrinsic components of mortality might have more impact on older ages than expected.

Irregularity of mortality patterns

Pakin and Hrisanov (1984) analyzed how well the *Gompertz-Makeham* model fits between age 35 to 75 by using the life table data of 35 countries. They found that the age pattern of the log-mortality curve is more complex than a simple linear function. The mortality pattern breaks at a certain point for most of the countries used in the study and may show substantial differences between the sexes (see Figure 5.2). The characteristic of the curve in Figure 5.2 cannot be described by the Gompertz-Makeham *law*. Hence, the non-Gompertz component is neither constant nor negligibly small. Especially for women it seems that mortality can be described by two exponential lines with different slopes. Pakin and Hrisanov (1984) interpreted their results with selection processes in the male population and hormonal rearrangement in the female population. Another explanation may be that the male mortality trajectory stems from cardiovascular diseases. Cardiovascular diseases afflict men at a greater rate than women (Wingard 1984), probably driven by late effects of tobacco consumption (Waldron 1993). The female pattern may also be a consequence of

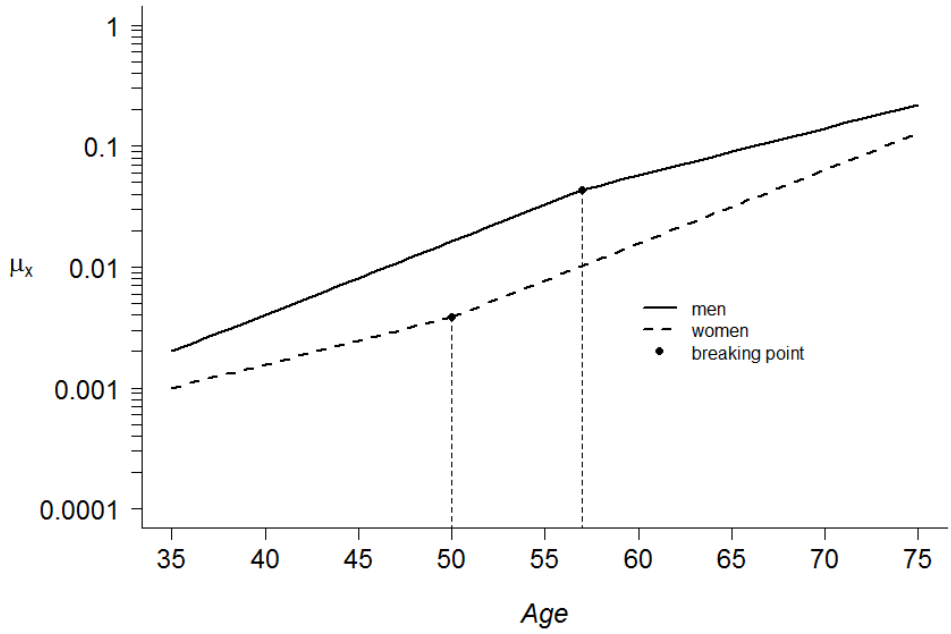

Figure 5.2. Schematic representation of the typical mortality curve on a semi-logarithmic scale (source: Pakin and Hrisanov 1984).

behavioral patterns, which change over age. Such patterns might be masked for the male population. Horiuchi and colleagues (2003) found a similar irregular mortality pattern in the middle-aged and older-aged French population (1979-1994). The authors argue that interaction effects of age changes in behavioral and environmental risks may account for this trend.

Exponential Pattern of Extrinsic Causes of Death

Carnes and colleagues (2006) estimated the non-Gompertz component by dividing causes of death data into extrinsic and intrinsic categories. The idea behind this method was to prove that such categorization reflects the two components of the Gompertz-Makeham *law*. They actually showed that intrinsic causes of death follow a Gompertz pattern. However, extrinsic mortality is not age-independent, but tends to increase exponentially over age with a smaller slope than the intrinsic component (Figure 5.3).

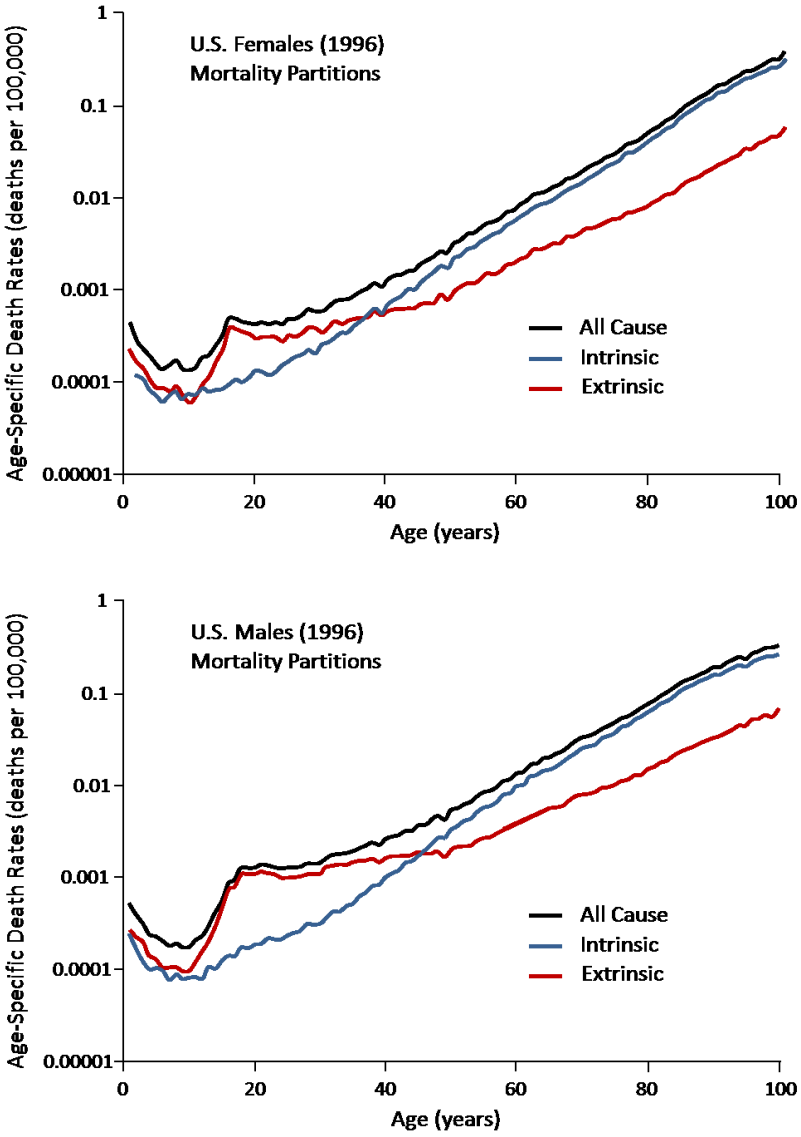

Figure 5.3. All-cause mortality partitioned into an extrinsic and intrinsic component by extrinsic and intrinsic causes of death. (source: Carnes et al. 2006).

A critical point, however, is that "*a perfect partition is not attainable*" as the authors state, because deaths may result from the interplay of extrinsic and intrinsic processes. This interplay impedes the classification of single causes of deaths into intrinsic and extrinsic categories and challenges the partitioning concept. At least, the partition of mortality by causes of death indicates that the mortality models should be reevaluated with special emphasis on an age increasing non-Gompertz mortality pattern. Classic mortality models, such as the Gompertz-Makeham or Heligman-Pollard model, clearly distinguish between an extrinsic and intrinsic mortality component and, thus, need a reevaluation. According to Carnes et al.

(2006), intrinsic mortality follows a typical Gompertz shape at adult ages (Figure 5.3). The extrinsic component is responsible for the mortality hump in adolescent and young adults and increases exponentially over age. Moreover, the study implies that the straight partition between extrinsic and intrinsic mortality is questionable for human populations. A possible explanation for the finding is that extrinsic risk declines over age and counteracts the acceleration of mortality rates.

Age Pattern of the Gompertz-Residuals

In order to test the findings of Carnes et al. (2006), a preliminary study is presented here to estimate the shape of extrinsic mortality. For this purpose, a frailty model with a Gompertz baseline hazard was fitted to mortality between ages 80 and 105. In this old age group, the extrinsic component should be negligibly small and intrinsic mortality should account for almost all deaths. At younger ages, the extrinsic component should become larger until it accounts for almost all deaths at younger ages. If the Gompertz component is stable over age, the residuals of the extrapolated model fit can be interpreted as the extrinsic mortality component. A frailty model is used for the analysis, since selection processes account for a deceleration of mortality at advanced ages (Beard 1959). According to Vaupel et al. (1979), the force of mortality for an individual at age *x* can be expressed as

$$\mu(x|Z) = Z\mu(x) \qquad (5.5)$$

with *Z* accounting for unobserved heterogeneity among individuals. A more detailed discussion about the *γ-Gompertz* frailty model with an additional analytical solution to estimate life expectancy can be found in Missov & Lenart (2013). By definition, the standard individual has a *Z* of 1.

$$\mu(x|1) = \mu(x) \qquad (5.6)$$

A certain population is defined by the sum of individuals with different frailties following a γ-distribution around 1 (Vaupel et al. 1979). Individuals with a *Z* value bigger than 1 suffer from a higher mortality risk, and vice versa. If *μ(x)* is Gompertz distributed (5.2), then the force of mortality in a certain period *y* may be expressed as

$$\bar{\mu}(x,y) = a(y)e^{b(y)x}s(x,y-x)^{\gamma(y)}, \qquad (5.7)$$

with *s* being the survival of the cohort born in year *y*-*x*. The γ-Gompertz model (5.7) is fitted to Swedish mortality for males and females ages 80 to 105. Next, the model fit is extrapolated for the age range 40 to 80 to estimate the residuals between the Gompertz fit and the data.

Figure 5.4 shows the difference between the model fit and the real Swedish mortality in 2011, which describes an exponential curve. After age 70 the difference decelerates and declines. The decline is given by the estimation method, since the residuals become very small after age 80. Nevertheless, between the ages 40 to 70 the residuals are approximately exponential with a smaller slope than the γ-Gompertz part. Moreover, the shape of the residuals approximates the age pattern of extrinsic mortality estimated by Carnes et al. (2006).

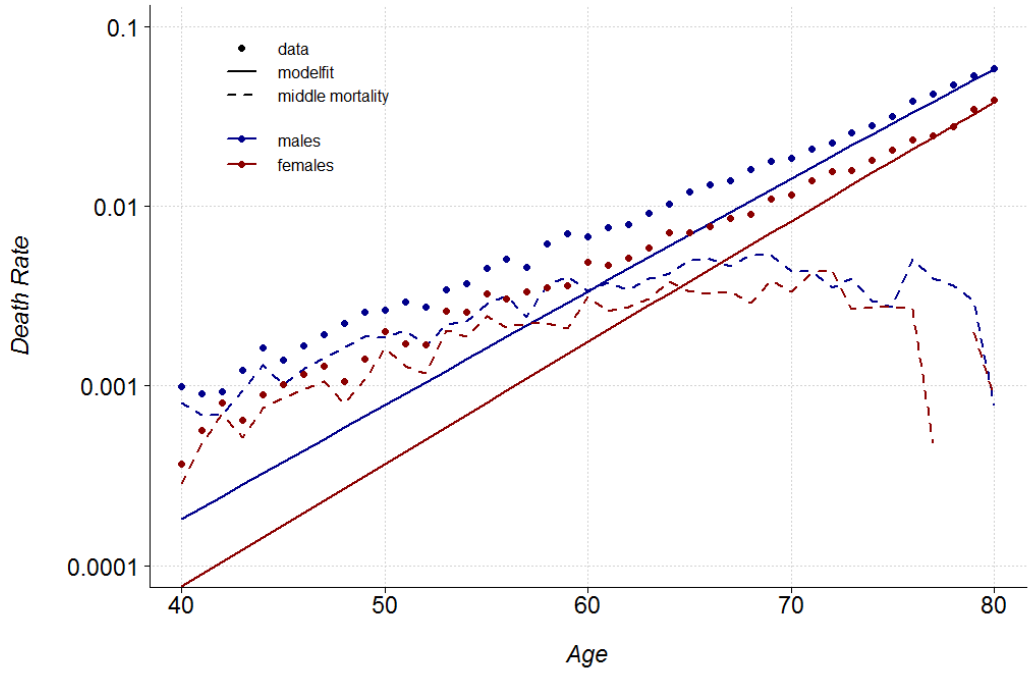

Figure 5.4. Middle mortality (MM), calculated by the difference between model fit and data for Swedish males and females in 2011 (source: www.humanmortality.org). MM shows an inverse bathtub-shape over age. (γ-Gompertz model fit: Males: a= 0.064, b = 0.147; γ = 0.14; Females: a= 0.041, b = 0.157; γ = 0.17).

Sweden is a modern industrialized country with a high standard of living, health insurance, stable social and economic system and was not directly involved in the Second World War. Newborn males can expect to live 79.8 and females 83.7 years. Even though it should be expected that most people die at old age due to intrinsic causes, it seems that Swedish mortality does not follow a straight line on a semi-logarithmic scale. The analysis of the residuals implies, that the extrinsic component is not age independent as the Makeham model suggests, nor negligibly small at adult ages as Thiele (1871) or Heligman and Pollard (1980) proposed. Due to its exponential pattern, the interaction of intrinsic and extrinsic risk factors could provide an explanatory framework. If physiological aging patterns are constant over age, only extrinsic risk factors may account for the different slope of the two components. Moreover, the extrinsic risk factor driving the non-Gompertz component can be assumed to decline over age and counteract the mortality increase due to intrinsic risk factors.

5.4 A New Model Based on Middle Mortality

The findings presented above illustrate that adult age mortality is unlikely to follow a Gompertz-Makeham pattern. If mortality is partitioned into an intrinsic and an extrinsic component by cause of death, the extrinsic component increases exponentially over adult age (Carnes et al. 2006). This is in accordance with the age pattern of the non-Gompertz residuals. Therefore, *middle mortality* may be driven by the same biological aging processes as the Gompertz component. However, some other factors decelerate the age increase of the *middle mortality* component. Selection may serve as a determinant, but is not likely to be due to the relatively low level of *middle mortality*. This is why selection processes become visible only at very old ages when mortality is high. Thus, the age change in extrinsic risk factors may be a more reasonable mechanism.

5.4.1 Avoidable and Unavoidable Deaths

The Gompertz model can be interpreted as a baseline force of mortality at a certain age, by definition age 0 ($a=\mu(0)$), which increases due to senescence at each age step, reflected by e^{bx}. It may be then that $\mu(0)$ is a consequence of the interaction of internal and external risk factors. The external risk factors are called here *avoidable*, which means that an individual can survive such events depending on its physiological constitution. This is more likely for younger individuals. Deaths at age 0 are due to an interaction of environmental hazards and resistance to such hazards. If the environmental risk does not change, the death rates in the next and subsequent age years ($\mu(1,2,3,\ldots,\omega)$) are only determined by senescence processes. In such case, it can be stated that $\mu(x) = \mu(0)e^{bx}$, which is the classic Gompertz model. For example, dysregulation in immune function causes an increase in age-specific susceptibility and death rates due to infectious diseases (Castle 2000). If exposure to infectious diseases is constant over age, the slope parameter in the Gompertz *law* reflects the *rate of senescence* of the immune system. Hence, the Gompertz *law* reflects *avoidable* deaths, since individuals may escape death at younger age. However, it only holds for a hypothetical population and is only approximately applicable to real populations.

Deaths following a Makeham pattern can be summarized as *unavoidable* deaths. *Unavoidable* deaths are defined here as deaths due to irresistible extrinsic events, independent of aging processes. A simple example for an *unavoidable* cause of death is a plane crash. Plane crashes are usually lethal for all passengers, because of their severity. The individual physiological constitution does not determine whether a passenger survives. Note, that Makeham only included age-independent *unavoidable* deaths, but such deaths can also have a certain age pattern: Imagine that the age structure of the passengers may not be random. For example, young passengers are attracted by low-cost carriers for financial purposes, whereas the elderly prefer more comfort and are willing to spend more money (see O'Connel and Williams 2005). Hence, the force of mortality due to plane crashes may change over age. In the following analysis, *unavoidable* deaths, though, are not considered, since it can be assumed that the amount of deaths from such causes is negligibly small or only occurs in young adulthood.

5.4.2 Interaction between Intrinsic and Avoidable Risk

The question is: What happens, if *avoidable* environmental risk factors change over age? Actually, the slope in death rates would reflect in some part changes in physiological aging, and in another part changes in *avoidable* extrinsic risk factors. This is a crucial point, since the classic mechanistic interpretation assumes a constant extrinsic risk. However, the human life course is characterized by changes. From childhood to puberty, early adulthood to middle and finally old age, the individual faces different situations and takes different risks to achieve individual goals.

For example, adolescents are at significant higher risk of being involved in a traffic accident compared to elderly drivers. This is due to a subjective underestimation of crash-risk, an overestimation of their own capability to deal in traffic and a self-perceived higher gain from risk taking (Harré 2000). The prominent *accident hump* around age 20 in most westernized countries is mainly due to motor-vehicle accidents (Lam 2002), which are one of the major threats of injury in Westernized countries (Evans 1991) and the fourth largest cause for disability adjusted life years lost (Murray & Lopez 1996). After years of adolescence, the involvement rate in traffic accidents steadily declines over age and is lowest among the older population (Hakamis-Blomqvist et al. 2002, Kent et al. 2009). Reasons for the age decline in traffic accident rates are mainly due to an increase in experience (Clarke et al. 2006) and a decline in reckless driving (Krahé and Fenske 2002). Moreover, the elderly population is less mobile and this reduces the risk of their being involved in traffic accidents (Marottoli et al. 1993). However, older individuals suffer from a lower survival probability from the same crash severity compared to younger individuals (Evans 2001). Both factors, the decline of involvement rate and increase of fragility due to physiological aging, mainly account for a U-shape in mortality rates by traffic accidents (Massie et al. 1995, 1997). Additionally, many psychological studies show that behavioral risk factors decline over age and may contribute not only to traffic accidents, but also to risk exposure in general.

5.4.3 Age Decline in Recklessness

In a more general sense, it can be assumed that risk-taking behavior not only affects exposure to traffic accidents, but exposes the individuals to other kinds of risks. For example, a study which analyzed behavior in a gambling game found that the probability for risky bets declines over age in both sexes (Deakin et al. 2004). It has been found that reckless behavior, quantified by the *Sensation Seeking Score* (SSS), declines over age (Zuckerman 1978, 1980, Haapasalo 1980, Krahé and Fenske 2002). Moreover, the SSS is positively related to risky driving (Harris & Houston 2010, Jonah 1997), injury risk (Turner 2004) and the intensity of alcohol consumption (Cherpitel 1993). These studies fit into the biological framework that age changes in risk-taking and aggression in humans evolved as a consequence of the trade-off between mating and child-rearing (Gangestad and Simpson 2000). At young adult ages investment is focused on mating, which increases risk-taking behavior especially in males. At middle adult ages the focus shifts to parental care, since investing in offspring survival is more beneficial than investing in new mating opportunities. Conclusively, the population shifts from reckless to risk-avoiding behavior with age. In support of this, testosterone levels, which are associated with recklessness and aggression (Alvergne et al. 2009, Archer 2006), tend to decline over age (Harman et al. 2001). Moreover, married men and fathers show lower testosterone levels compared to unmarried and childless men (Booth&Dabbs 1993, Gettler et al. 2011, Gray 2003, Kuzawa et al. 2009).

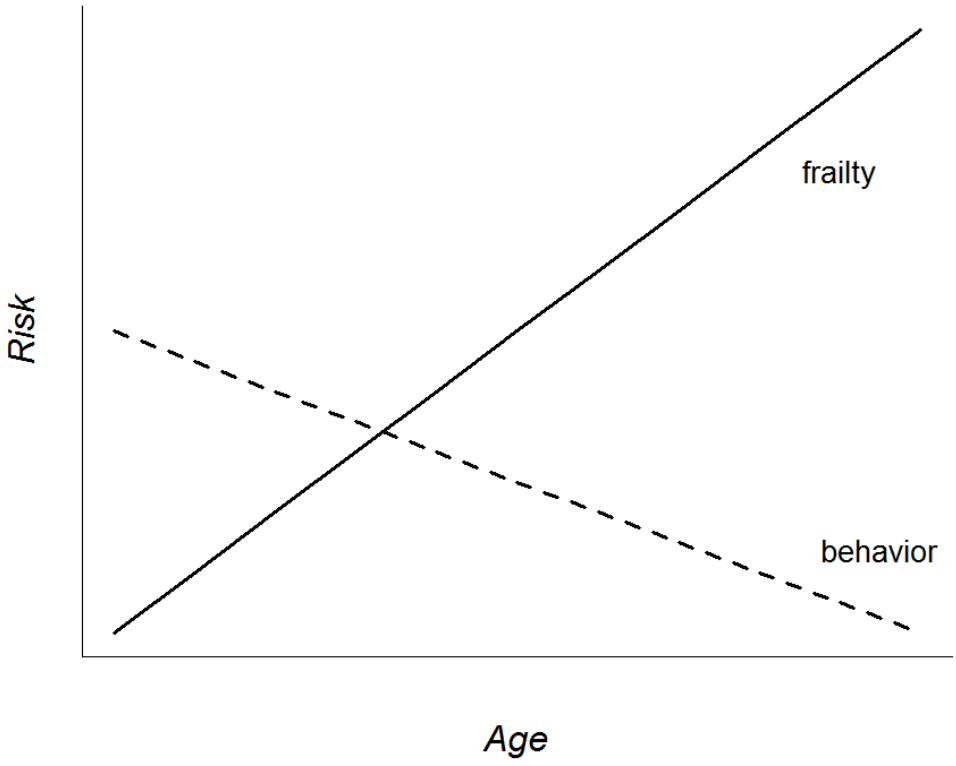

Figure 5.5. Schematic illustration of the age patterns of intrinsic and extrinsic risk factors. Whereas frailty increases over age due to the deterioration of physiological function, behavioral risk declines due to hormonal and social changes. The resulting age pattern of mortality rates is driven by both mechanisms and defined as middle mortality.

As illustrated, behavioral risk patterns may account for a substantial part of *middle mortality*. The interaction of risky behavior and physiological aging shapes the age pattern of *middle mortality* and may explain the findings in the previous sections. Given this, the classic extrinsic mortality component may underestimate mortality at middle and even old ages. Since behavioral risk declines over age, it may be expressed as $e^{-\kappa x}$. 'Behavioral' mortality is a product of senescent and behavioral risk (Figure 5.5). It can be expressed as $\mu(x) = \mu(0)e^{(b-\kappa)x}$, a relationship, which fits into the empirical findings on *middle mortality*.

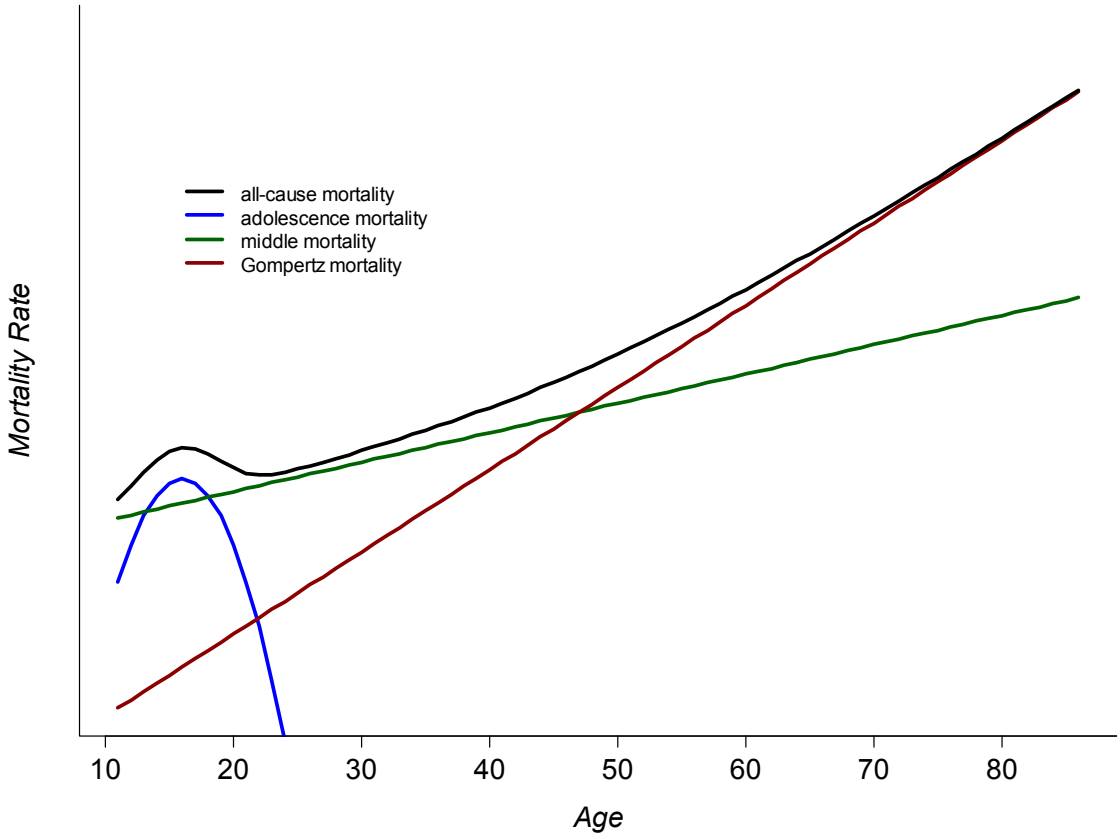

Figure 5.6. Schematic illustration of how the age pattern of mortality could be shaped by different mortality components. Adolescence mortality accounts for the mortality hump and becomes negligibly small at middle and old adult age. After age 30, the age pattern of all-cause mortality is affected by middle mortality and the Gompertz mortality.

To summarize, adult age mortality may be simplified to be the sum of three components: adolescence mortality (due to *unavoidable* risk at young age), middle mortality (driven by *avoidable* age-dependent extrinsic risk factors), and the Gompertz mortality (driven by of *avoidable* age-independent extrinsic risk factors) (Figure 5.6). The distinction between adolescence mortality and MM at young adult age is difficult and probably impossible by using all-cause mortality data. Hence, a better way to estimate MM is to focus on age groups when adolescent mortality is small. It can be assumed that this is the case after age 30-40.

5.5 Conclusion

The concept of extrinsic mortality is unlikely to reflect real underlying mechanisms. It is rather that adult age mortality results from the interaction between intrinsic and extrinsic risk factors. Since intrinsic factors permanently increase over age, extrinsic risk factors can be separated into a constant and declining part. The constant part includes environmental hazards, such as infectious diseases, and is represented in the Gompertz component. The age declining component traces back to behavioral risk factors, and to some age specific environmental risk factors. Findings in psychological and biological studies support this concept. Mortality, which results from the interaction of age-dependent risk factors, such as behavior, will in this study be called *middle mortality* (MM). Total adult age mortality is probably a result of Gompertz mortality and MM, both characterized by different exponential slopes. Hence, the classic Makeham term reflecting age-independent mortality is probably quite small. In the next chapter, a mathematical relationship will be developed, which incorporates the interactive risk model.

Chapter 6

The κ-γ-Gompertz Model: Estimating Sex Differences in Middle Mortality

6.1 Introduction

6.1.1 Sex Differentials in Mortality

It is well documented that in most human populations for which respective vitality data exist, male death rates exceed that of females at virtually every single age year. The sex differential in mortality has been attributed mainly to sex differences in behavior, which lead to different extrinsic risk profiles (see Chapter 2, Rogers et al. 2010). These risk profiles are culture- and country-specific as well as time variant. For example, 15 year old Russian males faced a 12.6 year lower life expectancy than females in 2000-09, whereas German females lived 5 years longer than their counter sex. Excess mortality rate among Russian males is caused by uncommonly high alcohol and tobacco consumption (McCartney et al. 2011). In general, premature deaths due to risky male behavioral patterns are universal and related to higher rates of homicide (Gartner et al. 1990), suicide (Möller-Leimkühler 2003), drug abuse (Rehm et al. 2006) and traffic accidents (Wilson and Daly 1985). Such behavioral patterns may account for the age pattern of sex differentials in mortality (see Chapter 3). If risky behavior is a function of age, this should then affect sex differentials in age-specific mortality rates in industrialized countries. The traffic accident rate is a good example of such an age-specific behavioral risk factor, as it is mainly attributable to reckless driving. In general, accident rates decline over adult age, and males are much more exposed to such threats than are females (Massie et al. 1995, 1997). Moreover, males behave more recklessly in all daily activities. Such risk factors may have an impact on mortality trajectories from middle up to old adult age and accelerate or decelerate the rate of mortality increase. Therefore, age-dependent behavioral risk patterns might mask mortality change due to senescence and should be considered in a biological framework. However, the most commonly used mortality models do not consider any age pattern of behavioral risk.

6.1.2 The Need for an Explanatory Mortality Model

Models about male and female mortality differences may be important to identify age and sex-specific risk factors and to forecast future mortality trends. Behavioral risk is the key factor in explaining the sex gap, but it is barely considered in classic approaches of modeling adult age mortality. In the previous chapter an argument for the incorporation of such risk factors into mortality modeling was made. Such a model will be presented and mathematically formulated in the present chapter.

Though behavioral risk factors decline over age, senescence leads to an increase in frailty. The interaction of both forces may lead to an age-increase, -decline or –constancy of a mortality component, called middle mortality (MM). In contrast to the classic Gompertz *law,* MM results from age-independent external risk factors interacting with senescence. The model presented here extends the Gompertz law by an MM component in order to give more detailed insight into mortality mechanisms. It will be tested, whether MM is a reasonable alternative to the commonly used age-independent Makeham-term. Moreover, MM might account for the rapid widening of the sex gap in life expectancy after World War II, which will also be studied.

6.1.3 The κ-γ-Gompertz Model of Mortality

Assume that the mortality hazard of an individual is determined by its aging process and *avoidable* risk factors. *Avoidable* risk factors are defined as the sum of hazardous events, which are more likely to be fatal with increasing age. For example, falling from a ladder may be painful at young, but lethal at old age. In contrast, *unavoidable* risk factors are defined as the sum of events. For reasons already mentioned (see Chapter 5), they will not be considered for the following model.

The Gompertz *law* reflects the situation when *avoidable* risk factors are age-independent and only senescence determines the slope of the mortality trajectory (note that selection processes or period and cohort effects are left out for simplification). As illustrated by empirical findings in the previous chapter, human mortality does not follow a straight Gompertz or Gompertz-Makeham pattern over

age. Age-specific behavioral risk patterns mainly account for this observation. To explain, behavior is assumed here to produce hazardous situations. They may be lethal in combination with the aging process. Hence, deaths depend on the physiological constitution and the severity of an external stressor, which is caused by behavioral risk. Of course, such events may change in severity or frequency or both. However, such distinction is not the subject of this work. A model which discusses such scenarios was developed by Li (2013). The criterion suggested here is far simpler: Risk due to reckless behavior declines exponentially over age. This reasoning is consistent with empirical findings of epidemiological and psychological studies as discussed in Chapter 5.

In conclusion, the concept of a pure distinction between extrinsic and intrinsic causes of death does not hold, except for in a few cases of *unavoidable* deaths. Such *unavoidable* deaths may happen to a higher extent in adolescence when reckless behavior is extremely pronounced (Arnett 1992) and leads to exceptionally high numbers of fatal accidents especially in motorized countries. Hence, the mortality hump at young age is likely due to *unavoidable* extrinsic stressors. The contribution of these stressors is, however, relatively small at middle and old adult age. Moreover, maternal deaths were higher in historical populations and may follow another age-trajectory. For both of the reasons above, the following model describes the force of mortality after age 40.

The model consists of two components: One is expressed by the Gompertz *law* and reflects senescence interacting with age-independent *avoidable* environmental risk factors. The second component reflects the interaction between age-dependent *avoidable* risk factors and *senescence* and is defined as MM, since it has its biggest effect at middle adult age. Hence, one can suggest that an individual's baseline force of mortality at each age x is the sum of two components:

$$\mu(x) = ae^{bx} + ce^{(b-\kappa)x}\,; a, b, c, \kappa \geq 0 \qquad (6.1)$$

The first component is the Gompertz-term, which reflects the increasing risk due to physiological aging (e^{bx}). The second component is the product of the behavioral risk ($e^{-\kappa x}$), which declines over age, and the risk due to physiological aging (e^{bx}). The product of $Ce^{-\kappa x}$ and ae^{bx} is the mathematical expression for MM (with $C*a=c$). If $\kappa<b$, MM increases over age and vice versa. The model reduces to

the Gompertz-Makeham (GM) model, if $\kappa=b$. Hence, the GM model is nested in the κ-Gompertz model.

The Gompertz term captures deaths unrelated to age-changing external stressors. Especially at old age, environmental factors which are beyond the control of individuals become more dominant in determining mortality rates. Hence, it is hypothesized here that MM is higher than Gompertz-like mortality among middle age individuals, but becomes less important at old age. At old age, mortality rates are also affected by selection processes. Since robust individuals are selected for in an aging population, the amount of heterogeneity in robustness accounts for a deceleration of the force of mortality at very old age (Beard 1959). Therefore, a proportional hazard model is assumed to reflect the selection process. This means that mortality curves differ between individuals in their level, but not in their slope. Vaupel and colleagues (1979) demonstrated that heterogeneity on a population level is best described by a γ-distribution, so that the average force of mortality($\overline{\mu}(x)$) is

$$\overline{\mu}(x) = \left(a(y)e^{b(y)x} + c(y)e^{(b(y)-\kappa(y))x}\right)s(x, y-x)^{\gamma};\ a, b, \gamma, c, \kappa \geq 0. \quad (6.2)$$

By assuming that $C*a=c$, equation (6.2) becomes

$$\overline{\mu}(x) = (a(y)e^{b(y)x}[1 + C(y)e^{-\kappa(y)x}])s(x, y-x)^{\gamma};\ a, b, \gamma, c, \kappa \geq 0. \quad (6.3)$$

Equation (6.2) allows the identification of both mortality parts separately, because in its case, both components reflect mortality rates. Equation (6.3) better describes the behavioral risk pattern, since the expression $Ce^{-\kappa x}$ only contains the age dimension and reflects the effects of behavioral risk on the Gompertz component.

To summarize, the model consists of two parts. First, the Gompertz component, which becomes important at very old age when frailty is high and deaths depend less on risk taking behavior, but more on age-independent environmental risk factors, like medical care and socioeconomic status. The second component reflects the interaction of risk-taking behavior and the mortality increase due to senescence. This component can be interpreted in terms of mortality due to declining risk-taking behavior, which counteracts the vitality decline due to physiological aging. In the case that $\kappa = b$, the κ-γ-Gompertz model is simplified to the γ-Gompertz-Makeham model:

$$\overline{\mu}(x) = \left(a(y)e^{b(y)x} + c(y)\right)s(x, y-x)^{\gamma};\ a, b, \gamma, c\ \geq 0 \qquad (6.4)$$

The γ-Gompertz-Makeham model is a special case and therefore nested in the κ-γ-Gompertz model. The *null hypothesis* states that the γ-Gompertz-Makeham model (null model) is sufficient to describe mortality dynamics, whereas the *alternative hypothesis* states that the mortality pattern follows the κ-γ-Gompertz model (alternative model). The null model is defined as the model with fewer explanatory variables compared to the alternative model. According to the principle of parsimony, the null model may be rejected, if the gain in information outweighs the additional explanatory variable (e.g. Wears 1999).

Parameter *a* is defined as reflecting age-independent *avoidable* environmental hazards, whereas the expression $ce^{-\kappa x}$ reflects age-dependent *avoidable* extrinsic risk factors mainly triggered by behavioral risk patterns. Both the Gompertz and the MM component compete for lives. If one component is high, the other one would fail or only take a few lives. If κ is equal or even higher than *b*, behavioral risk factors are outcompeted by age-independent environmental risk factors. This would also imply that age-independent risk factors are predominant at adult age. In such a case, the null model would be the best model and it would be impossible to examine whether MM is due to the interaction of *avoidable* extrinsic and intrinsic risk factors or due to age-independent *unavoidable* mortality. Moreover, the relative impact of both components on total mortality may change over time depending on the relative risk of age-dependent and age-independent extrinsic risk factors. Especially in Westernized countries, the contribution of each component may have changed due to medical improvements. It can be assumed that the Gompertz component was higher in the past due to the higher impact of a hazardous natural environment. The reduction in the Gompertz component probably causes the relative importance of the MM component increasing.

Another possible scenario could be that $\kappa = 0$. In that case, the κ-Gompertz component is approximately the Gompertz component. Behavioral changes in risk factors are unimportant and the κ-γ-Gompertz model is reduced to a simpler γ-Gompertz model. As regards sex differences in mortality, the model provides information about the extent to which behavioral factors, environmental risk or biological aging may play a role. The study has the following aims:

- To examine if age-dependent MM, driven by age-dependent extrinsic risks and senescence, serves as an alternative explanation for a constant extrinsic mortality component as defined in the classic Gompertz-Makeham model.
- To show that MM is generally higher in males compared to females, but declines faster over age in females.
- To show that MM mainly accounts for the variation in sex difference in life expectancy.
- To show that the κ-γ-Gompertz model reproduces the adult age pattern of the relative and the absolute sex differential in mortality.

6.2 Method

The hypothesis that the concept of MM reflects human mortality more appropriately than the commonly used Makeham term will be tested by using vitality statistics of seven countries spanning a maximum time period of 151 years (Denmark: 1945-2011, England & Wales: 1951-2011, France: 1926-2010, Italy: 1982-2009, Netherlands: 1960-2009, Norway: 1956-2009, Sweden: 1861-2011). The countries are chosen using the following criteria: 1. large population size; 2. vital statistics are available back at least to the nineteenth century. The second point is especially important, since the fraction of the cohort surviving from age 0 to age x is reconstructed by using information from period data. The data has to be traceable back to cohorts born 99 years before the period, which is analyzed to estimate the frailty model. Japanese data, for example, only stretch back to 1947, which makes it impossible to calculate cohort survival for recent periods. Death counts (D(x)) and person-years lived (E(x)) from the raw tables are used for all calculations. The data are from the Human Mortality Database (HMD) (www.humanmortality.org, 2013).

Since it was found in a preliminary study that the parameter estimates of the κ-γ-Gompertz model are highly sensitive to starting conditions (see Appendix C) some restrictions are applied to stabilize the model. In order to find reliable estimates for MM, parameters b and γ are fixed. Fixing b may be reasonable, since it is assumed, that "all older humans share a similar, and perhaps essentially the same, rate of increase in mortality with age" (Vaupel 2010, p. 539). To find a reasonable b value, parameter estimates from Missov (2013) are used. The author applied the γ-

Gompertz model to Swedish females and found parameter values ranging from 0.1 for the oldest (1891) to 0.14 for the most recent calendar year (2010). However, estimates for the calendar year 1891 can be assumed to be more affected by MM than estimates for recent years. Since MM or a comparable extrinsic mortality component have not been considered by Missov (e.g. by including a Makeham term into the model), b values of historical data are slightly underestimated. Hence, in this study b is set to 0.14 in order to use an estimate less affected by MM. For parameter γ it appears to be more difficult to find reliable estimates, since it is very sensitive to old age mortality when its effects become measurable. The problem with centenarian data is that only a few individuals are alive and, hence, statistical perturbations of the force of mortality are higher. For example, Missov (2013) found γ estimates between 0.1 and 0.14 in his study, whereas Manton et al. (1986) estimated γ to be around 0.29 for females and 0.21 for males. In order to find a reliable γ value, another approach is therefore applied, based on the auxiliary information from the force of mortality of supercentenarians (age 110+). Previous studies have shown that the force of mortality for this subpopulation is stable at a level of approximately 0.7 (Gampe 2010, Robine et al. 2005). The plateau approaches b/γ when it is assumed that mortality follows a κ-γ-Gompertz pattern (see Appendix 2). If b =0.14 and the plateau is around 0.7, γ can be assumed to be ~0.2. Moreover, a b of 0.14 best fits to the observed life expectancy (Appendix D). Since two parameters are fixed, the three non-fixed parameters of the κ-γ-Gompertz and the two parameters of the γ-Gompertz-Makeham model are estimated by using the maximum likelihood estimation method (see Appendix B).

According to the principle of parsimony, the model with the fewest variables and most information should be accepted. In terms of the number of variables, the γ-Gompertz-Makeham model should be preferable compared to the κ-γ-Gompertz model (6). However, if the information gain exceeds the penalty for an additional parameter, then the κ-γ-Gompertz model is favored. Since the γ-Gompertz-Makeham model is nested in the κ-γ-Gompertz model, a log ratio test can be performed to statistically test the hypothesis that the null model (γ-Gompertz-Makeham) should be preferred over the alternative model (κ-γ-Gompertz). The log-ratio test statistic (Θ_0 -> null model; Θ_1-> alternative model) is constructed as follows:

$$W = 2(logL(\Theta_1|x) - logL(\Theta_0|x); \Theta_1 \ni a_1, b_1, \gamma_1, c_1, \kappa;\ \Theta_0 \ni a_0, b_0, \gamma_0, c_0, \quad (6.5)$$

with W being the *generalized likelihood ratio statistics*. The null hypothesis $H_o: \Theta_1 = \Theta_0$ is tested by calibrating W with the χ^2 distribution with *degrees of freedom* = 1. If the p value for the χ^2 statistic is significant ($p \leq \alpha;\ \alpha = 0.05$), then the null hypothesis can be rejected and vice versa. This is done for each period in every country used in the study. To test the impact of MM on the sex gap, partial life expectancy (age 40-99) is calculated based on the κ-γ-Gompertz model for the selected countries and periods listed above. Additionally, the extent to which MM contributes to life expectancies in males and females and to the LE sex gap is examined. For this purpose, a single decrement life table is constructed (see Preston et al. 2001, p. 82-83) with MM eliminated and treated as a single cause of death for simplification. All calculations and figures were computed by using the free statistical programming language R (Version 3.01).

6.3 Results

6.3.1 Log-Ratio Test

The log-ratio test is significant for virtually all countries and periods, meaning that the null model (γ-Gompertz-Makeham) can be rejected in most cases. The alternative model (κ-γ-Gompertz) is less meaningful only for females living in France in the years 1995-98 and 2004-05, and in Italy in 2003, 2005 and 2007-09 (Figure 6.1).

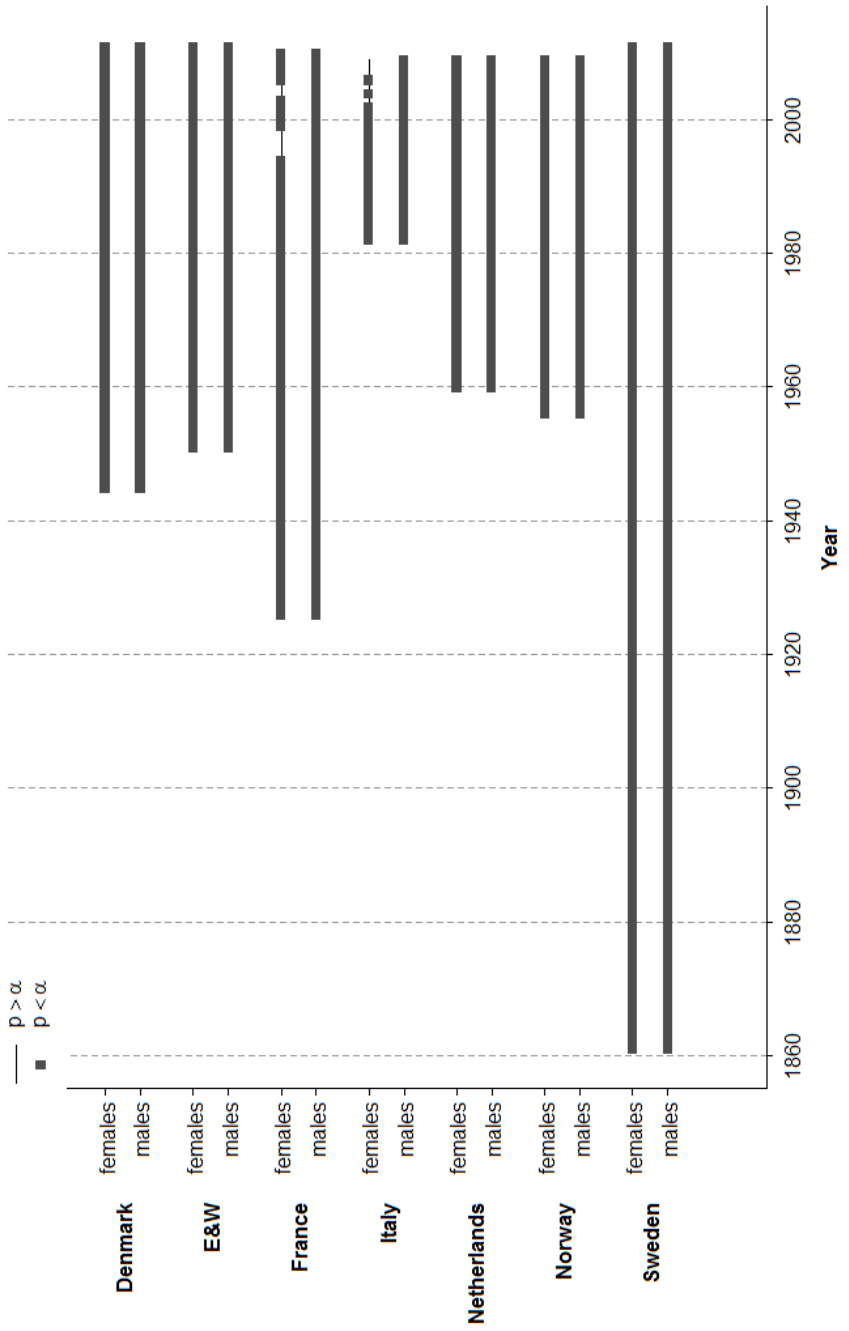

Figure 6.1. Log-ratio-test statistics for the seven countries examined in the study. The null model (γ-Gompertz-Makeham) can be rejected (indicated by bars) in all countries and periods except for some recent years for French and Italian females (indicated by lines).

6.3.2 Model Fit

Figure 6.2 shows the fitted lines of the κ-γ-Gompertz model for selected periods in Sweden. The model fit is very accurate for all, but especially for the recent periods. The model fit for 2011 shows a different pattern between years 40 and 60 compared to the data. This is especially the case for females, caused by an overestimation around age 40 and by an underestimation of mortality around age 55 (Figure 6.2). This pattern has also been identified for France and Sweden starting in the 1990s and is more pronounced in females.

The intercept of the Gompertz mortality (GM) component declined slowly during the past 150 years for both sexes (Figure 6.3). Between 1920 and 1950 the intercept, however, stagnated for both sexes. The slope of the GM is not changing due to the model's restrictions.

The MM component shows high variation in intercept and slope (Figure 6.4). In both sexes the intercept of MM continually drops from the late nineteenth to the early twenty-first century, even though it stagnates between 1950 and 1980 (for males only). In most periods MM increases exponentially over age. This increase decelerates and becomes a declining trend after age 80. This is in accordance with theoretical findings that the MM approaches 0 at very old age (see Appendix A).

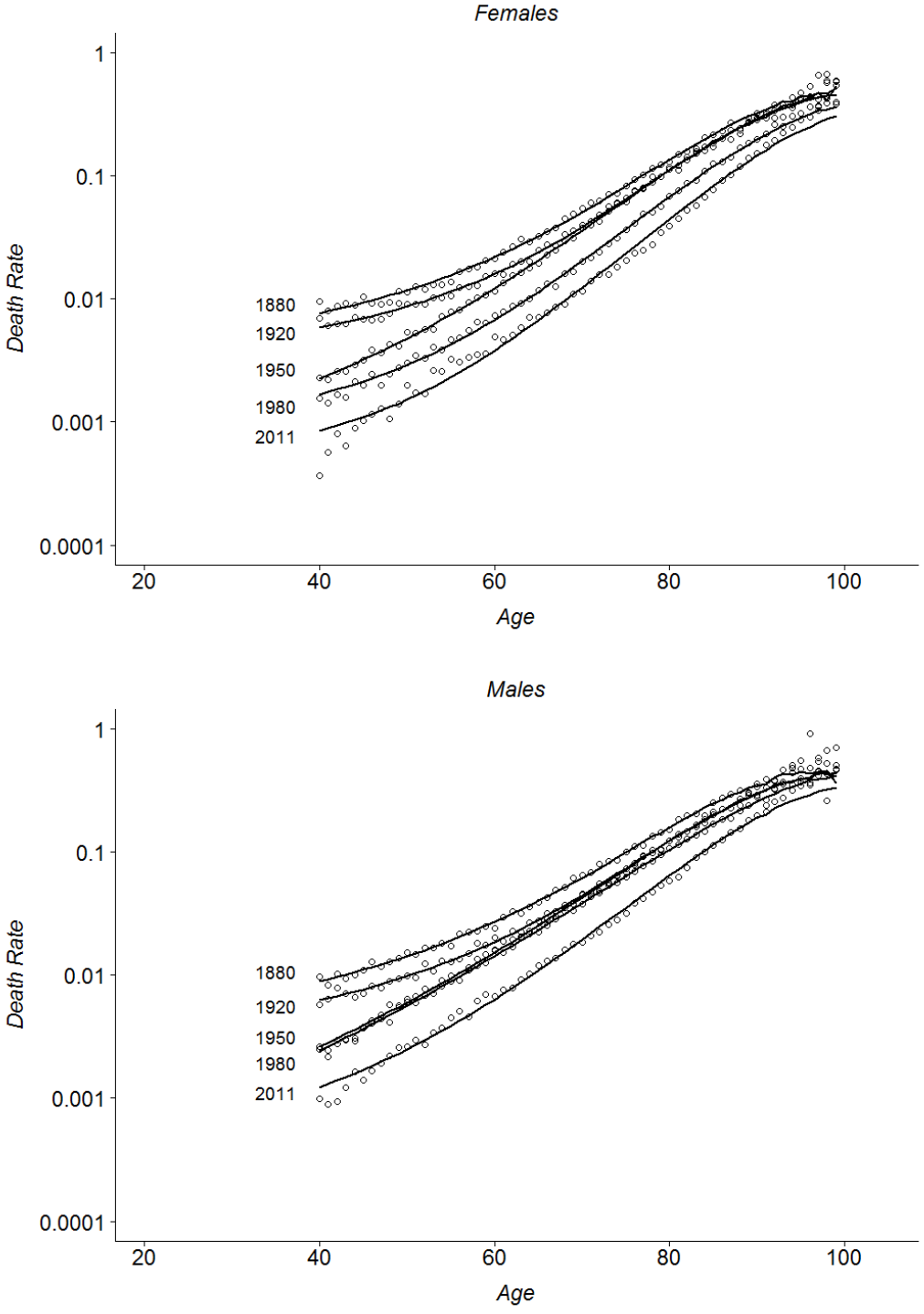

Figure 6.2. Time trend of the κ-γ-Gompertz model fit (lines) and observed mortality rates (dots) for Swedish females and males.

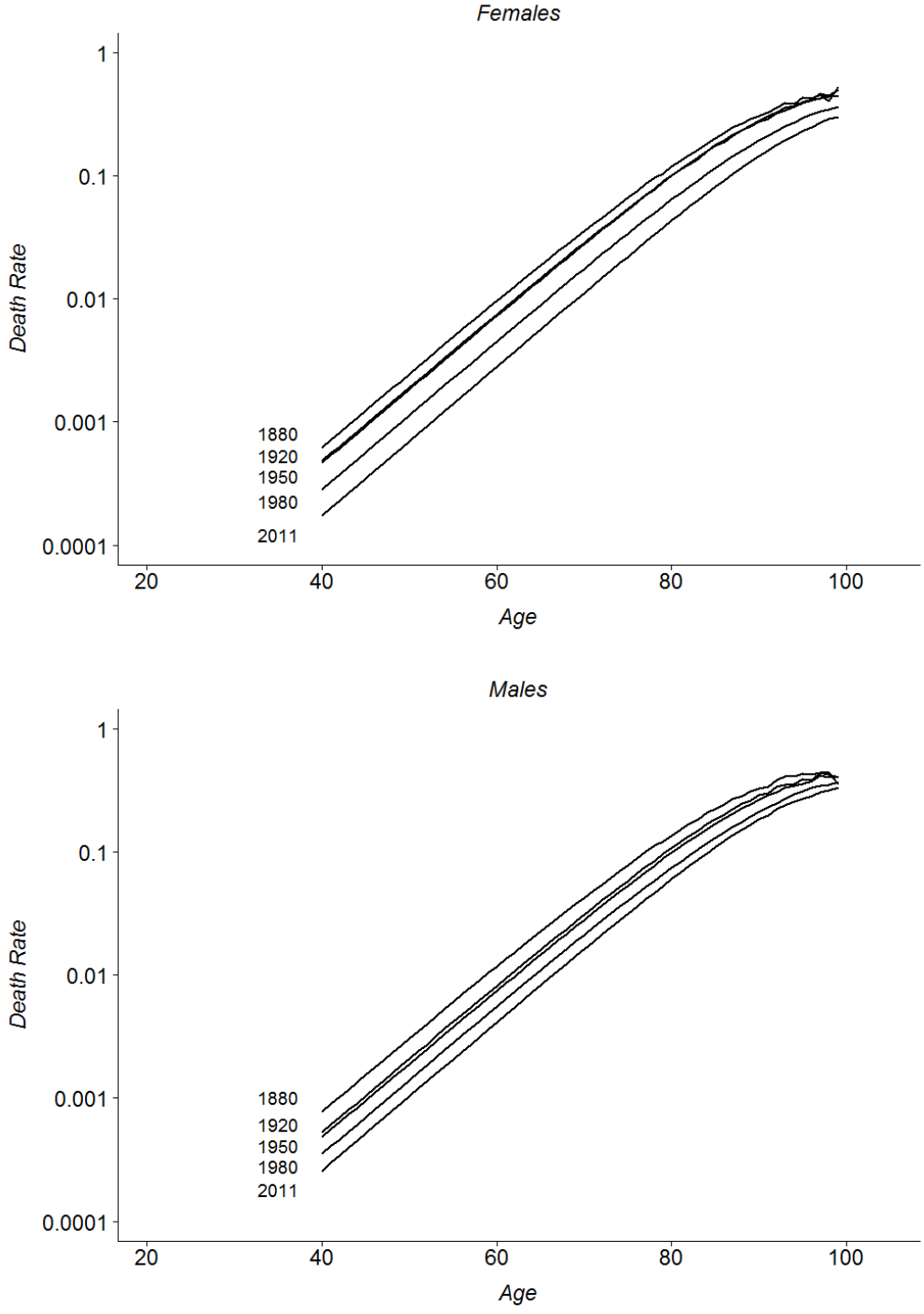

Figure 6.3. Time trend of Gompertz mortality for Swedish females and males.

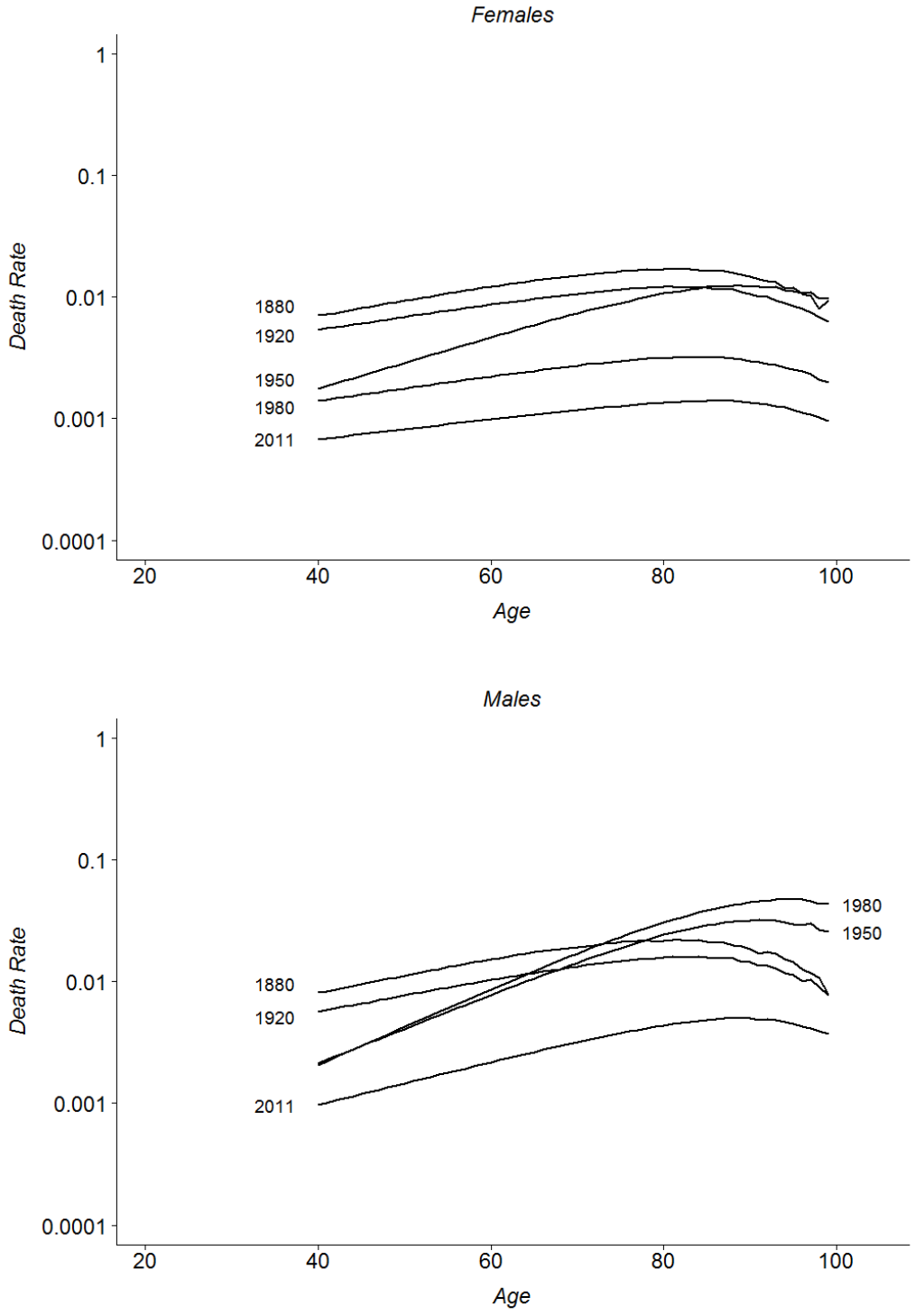

Figure 6.4. Time trend of the middle mortality component for Swedish females and males.

6.3.3 Parameter Estimates

Figure 6.5 shows the parameter estimates of the κ-γ-Gompertz model for Sweden. Intercept parameter *a* of GM is generally higher in males. However, the sex gap in the intercept narrows from the 1860s until the 1950s and becomes equal between the 1950s and 1970s and is even higher for females in some periods. After the 1970s, the sex gap in *a* starts to diverge mainly due to a deceleration of the falling trend for males between the 1970s and 1990s. In the late 1990s, the sex difference in parameter *a* converges again, since males start to catch up to the female intercept.

The intercept of the MM component, denoted by *c,* falls for both sexes over the past 150 years. The most pronounced sex gap with a higher *c* in males can be found in the nineteenth century. The sex gap steadily declines until the 1930s (Figure 6.5). In 1919 there is a remarkable increase for both sexes, probably due to the Spanish Flu. After the Second World War, parameter *c* stagnates in both sexes and even increases for males, causing a small hump with a maximum around the late 1970s. After the 1970s the sex gap in *c* diverges and remains at a constant small level until recent periods.

In contrast to the falling trend of the intercept parameters, the slope parameter κ experiences a more dynamic evolution throughout the past 160 years (Figure 6.5). Note that the slope of MM is b-κ. A high value of κ means a lower slope of MM and a smaller contribution of MM to total mortality. From 1861 to around 1900, κ increases in both sexes from around 0.1 to 0.12, meaning a MM slope between 0.02 and 0.04. Parameter κ is slightly higher in females than in males. Between the 1900s and the 1950s, κ declines to a minimum of around 0.08 in males and 0.09 in females. The slope of MM is higher than ever before that time. During the second half of the twentieth century, κ evolves very differently among males and females. Whereas κ continues to shrink in males until the 1960s and stays at around 0.06 until the late 1980s, female κ increases to around 0.11 in the 1970s and continues to slightly increase until the 2000s to 0.12. Hence, the impact of MM on total mortality at old age is higher for males than for females. After the 1980s, male κ increases more rapidly and approaches a level of around 0.1 in 2011.

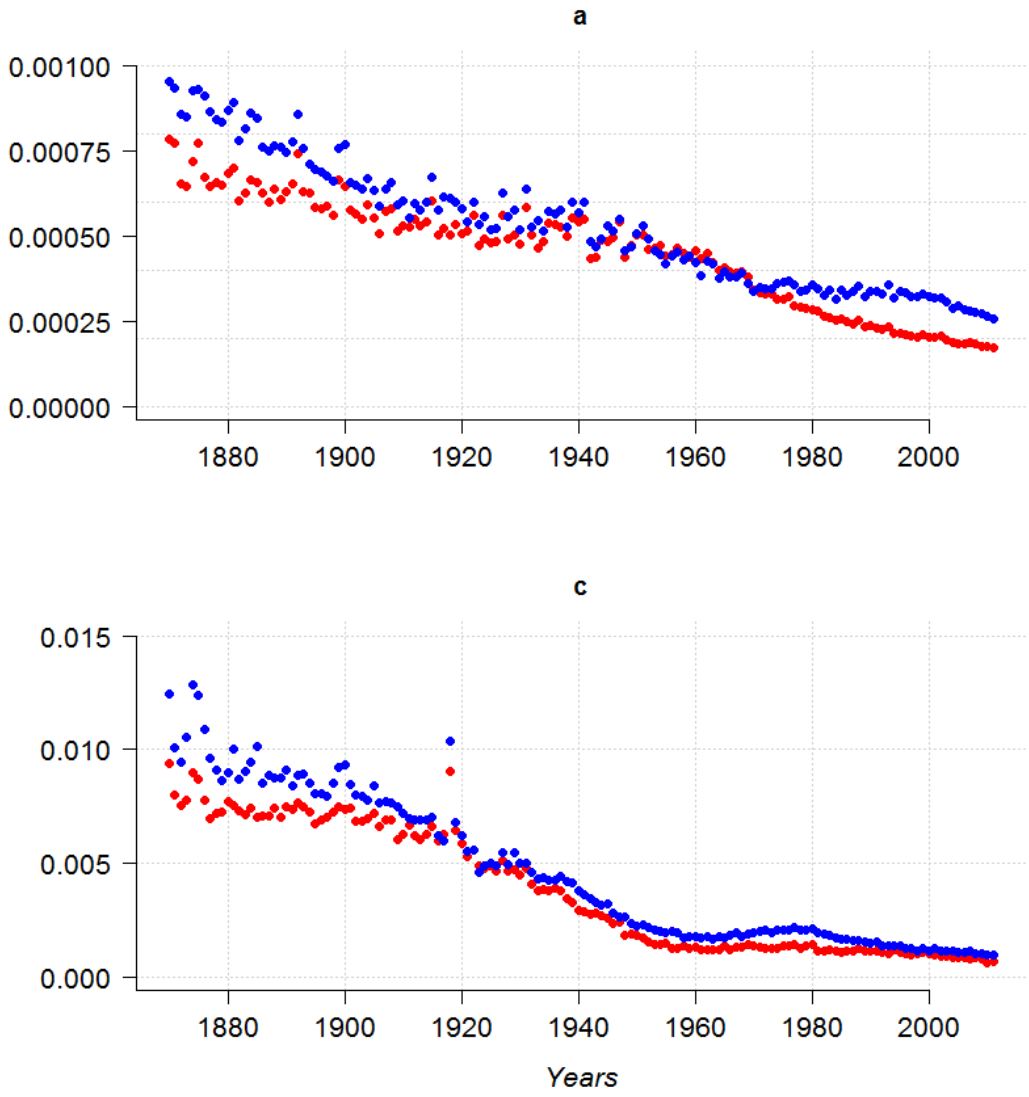

Figure 6.5. Time trend of the parameter estimates of the κ-γ-Gompertz model for Swedish females (red dots) and Swedish males (blue dots) between 1861 and 2011.

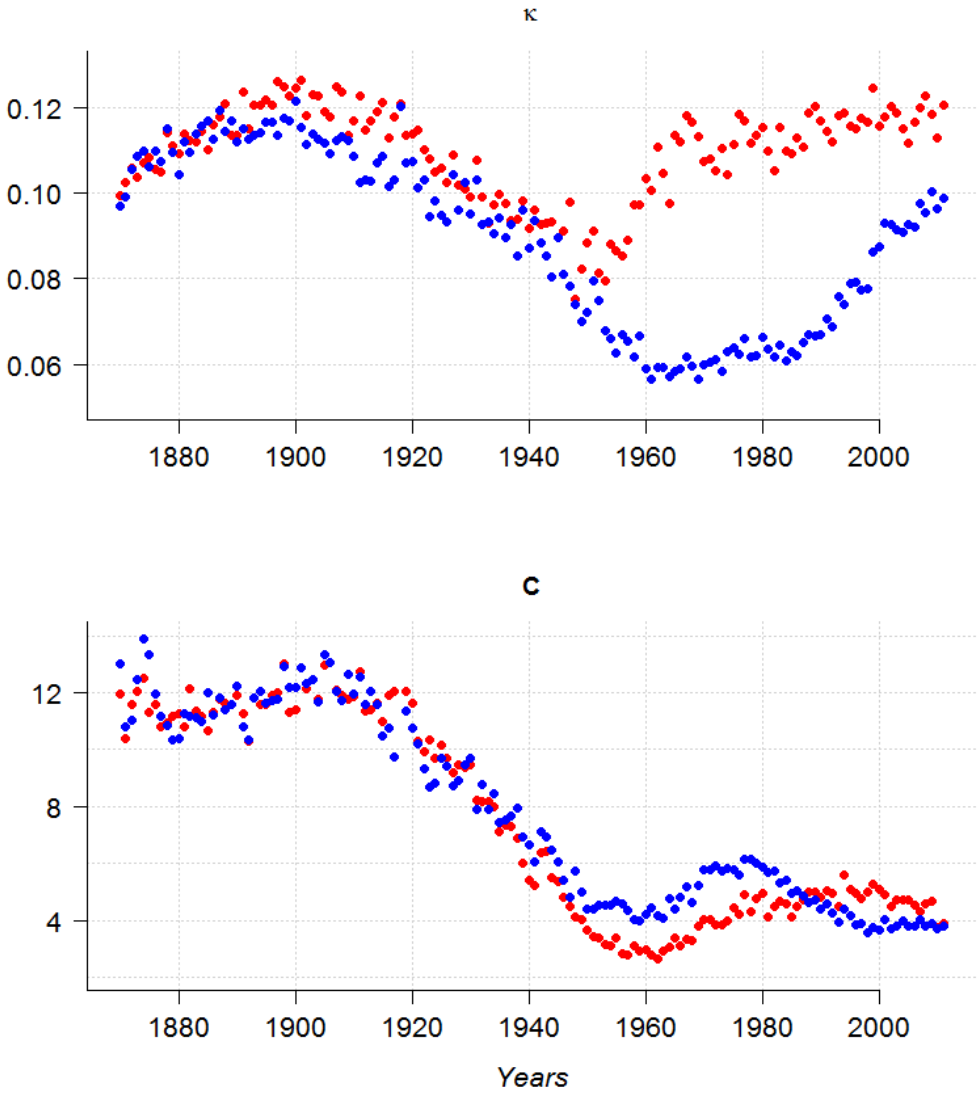

Figure 6.5. (continued)

Parameter *C* (is *c/a*, see equations 6.2 and 6.3) reflects the relative size of MM compared to GM at age 40. *C* is quite similar between males and females until the 1950s (Figure 6.5). It follows approximately the pattern of κ until the 1950s, even though the progress in *C* is very small until 1910. After 1950, parameter *C* diverges between the sexes resulting in a higher value for males. After 1990 the trend reverses and female *C* exceeds male *C*.

6.3.4 Middle mortality and the sex gap in mortality

Figures 6.6 to 6.11 show the model fits of the ratio and the difference between male and female mortality rates. The model retraces the flat trend of the ratio in the nineteenth and early twentieth century as well as the typical hump around age 50 to 60 reaching a climax in the 1980s. The absolute difference between male and female mortality increases exponentially over age, which is also captured by the κ-γ-Gompertz model. Even though the model fit is very accurate for both measures of the sex differential, there are some deviations in the real data, especially for the ratio in France and England & Wales (Figures 6.8 and 6.10).

For example, in 1980 and 2009 France the model slightly overestimates the peak of the ratio, and underestimates its trend after the peak. This is probably due to the irregular female mortality pattern between age 40 and 60, as discussed in the introduction to section 3.3. The κ-γ-Gompertz model overestimates mortality around age 40, but underestimates it around age 55.

Moreover, at old adult age the fit sometimes becomes slightly inaccurate for the difference. This is likely due to the fact that the model is restricted to a fixed γ and b value. This often leads to an underestimation of the real trend, so that the model predicts lower male than female mortality at old age. Apart from these deviations, the sex differential by the model fits the data quite accurately in all countries and periods, including those not discussed here.

Figure 6.6. Ratio of male to female mortality (dots) and the κ-γ-Gompertz model fit (line) in Sweden.

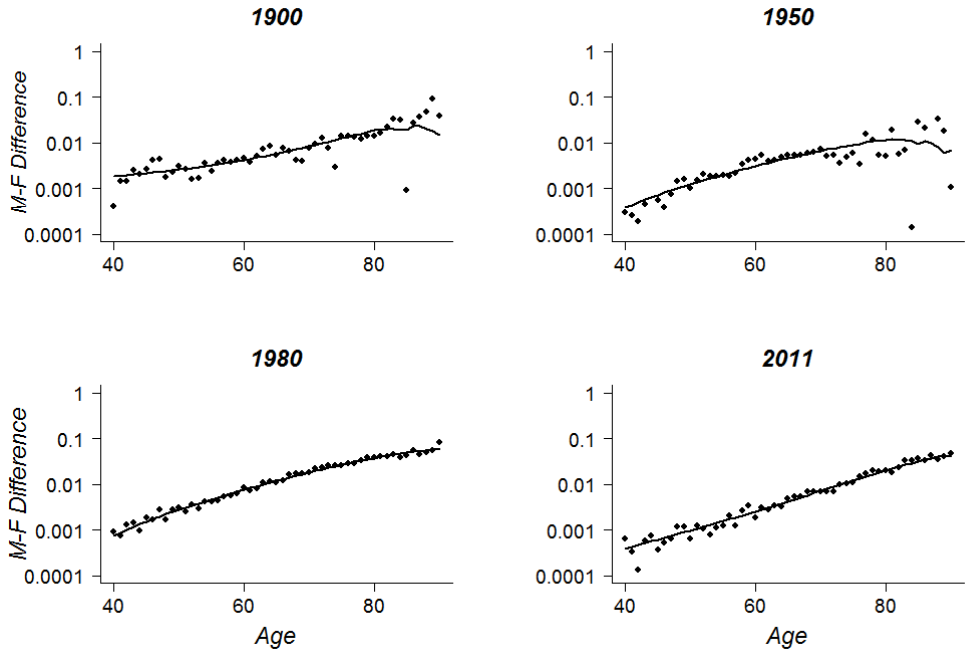

Figure 6.7. Difference between male and female mortality (dots) and the κ-γ-Gompertz model fit (line) in Sweden.

Figure 6.8. France; Ratio of male to female mortality (dots) and the κ-γ-Gompertz model fit (line) between ages 40 and 90.

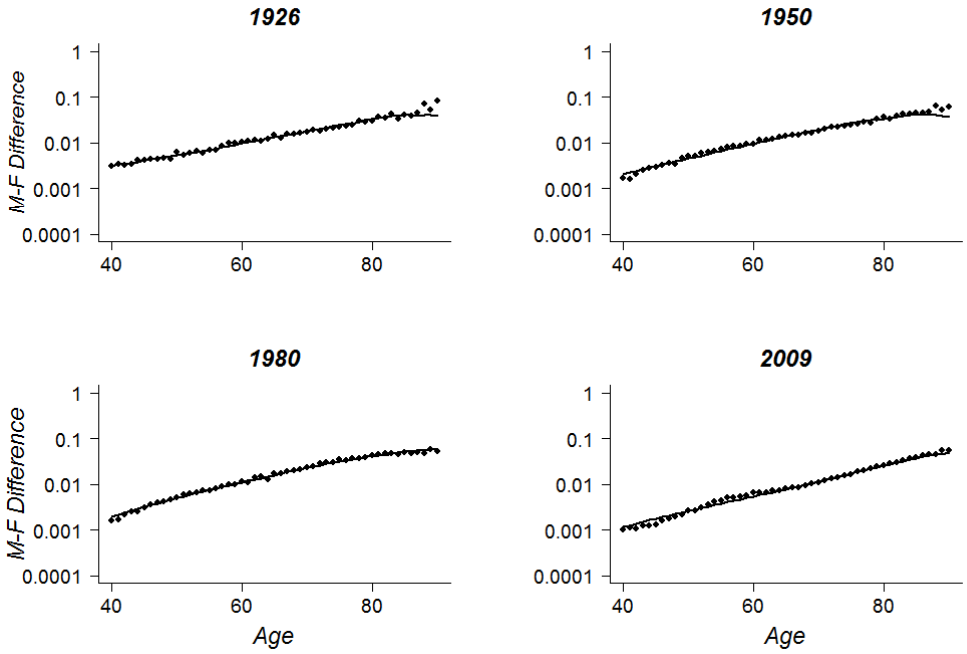

Figure 6.9. Difference between male and female mortality (dots) and the κ-γ-Gompertz model fit (line) between ages 40 and 90 in France.

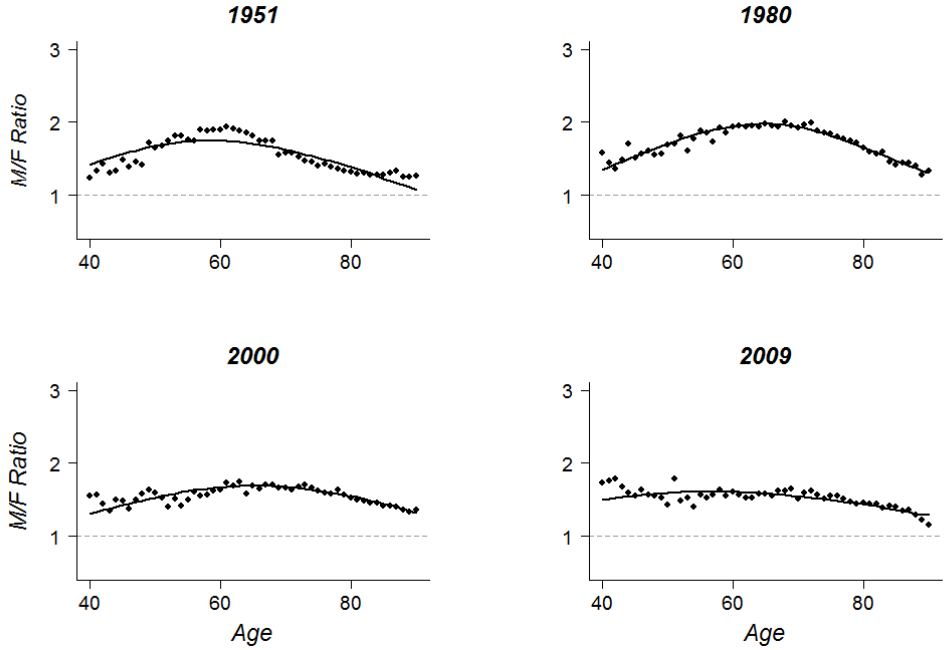

Figure 6.10.Ratio of male to female mortality (dots) and the κ-γ-Gompertz model fit (line) between ages 40 and 90 in England & Wales.

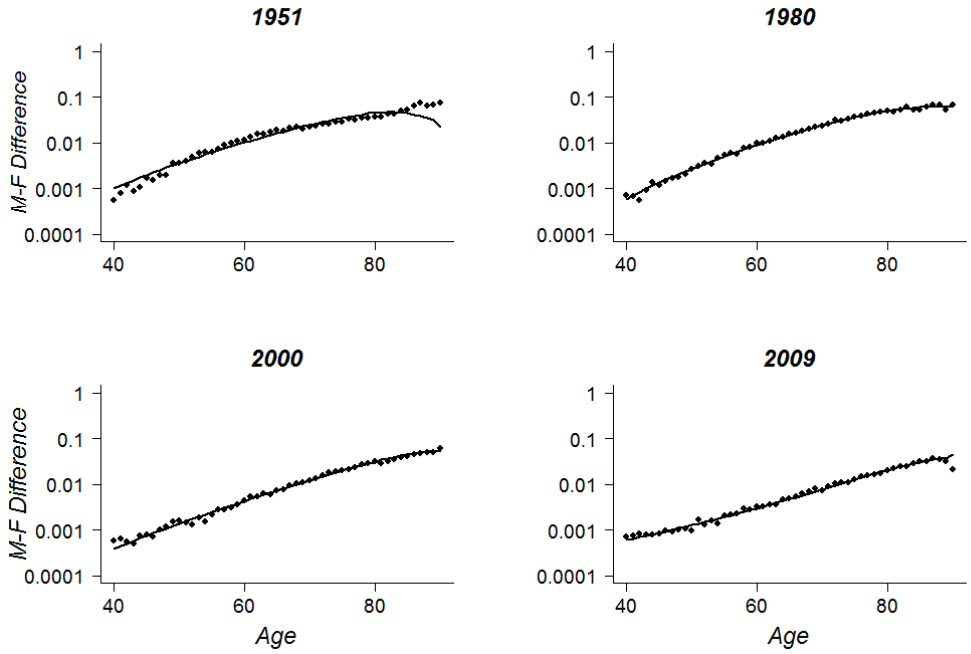

Figure 6.11. Difference between male and female mortality (dots) and the κ-γ-Gompertz model fit (line) between ages 40 and 90 in England & Wales.

6.3.5 Middle mortality and the sex gap in life expectancy

Based on the estimates of the κ-γ-Gompertz model, life expectancy (LE) at age 40 has increased in all countries over the past 150 years (Figure 6.12). In Sweden, LE increased from around 28 years for females and 26 years for males in the 1860s up to 43 years and 40 years, respectively, in 2011. After 1950 female LE increases approximately linearly in all countries, whereas the progress in male LE is delayed for around three decades and actually declined slightly in all countries except for England & Wales and France. However, the life expectancy in the two latter countries is approximately 3 years lower compared to the rest. Around the 1980s, male LE starts to increase linearly and is highest in Sweden (41 years) and lowest in Denmark (38 years) in 2011. For females the highest LE in the most recent period can be found in France (46 years) and the lowest in Denmark (42 years).

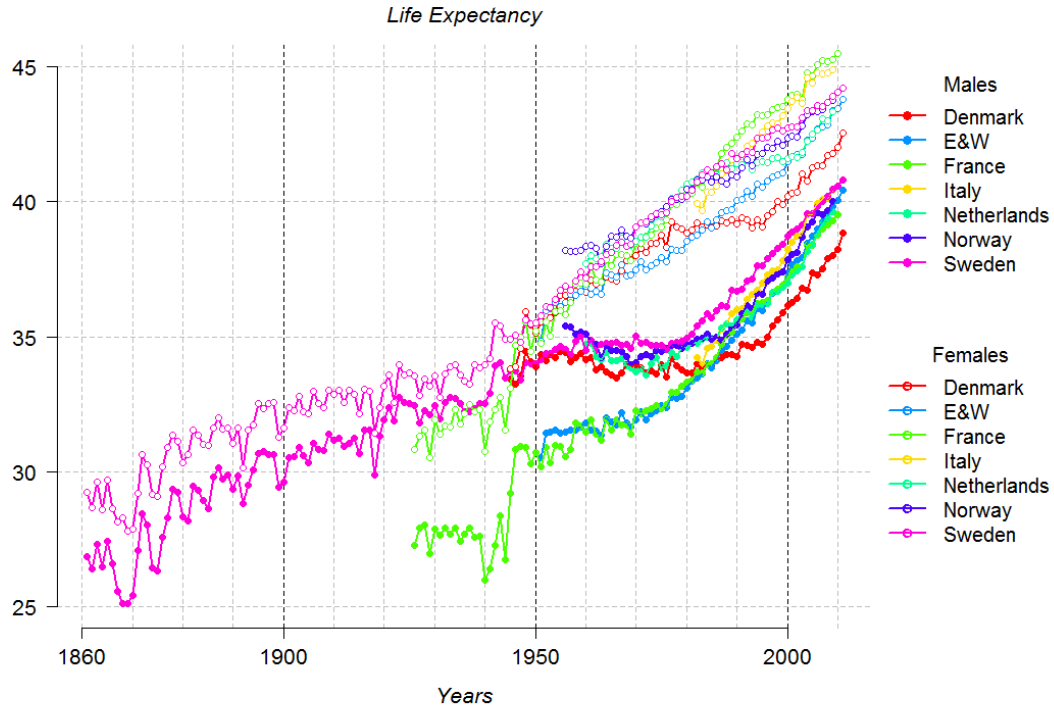

Figure 6.12. Life expectancy at age 40 calculated from the κ-γ-Gompertz model.

Figures 6.13 to 6.15 show the LE at age 40, if MM were eliminated in males and females. In Sweden, the contribution of MM to LE loss is lowest compared to all other male populations. It declines from 9 years in the 1860s to 4 years in 1950 (Figure 6.13). In Swedish females the impact of MM has been around one year less

until 1950 compared to males (Figure 6.15). After 1950 the impact of MM on male LE increases in all countries and is highest between the 1970s and 1990s depending on the country (Figures 6.13 and 6.14). England & Wales and the Netherlands have particularly high MM in the second half of the twentieth century. In England & Wales MM is highest in 1969 and accounts for 38 life years lost, and in the Netherlands for 30 years lost between 1979 and 1984. The trend in MM for these two countries is due to an overestimation of the MM component (Figure 6.16). This is, because the mortality curve follows a concave pattern in males. Therefore, England & Wales and the Netherlands were not considered for the calculation of the sex gap in LE with MM eliminated (Figure 6.17). The male population in the other five countries shows a high variation in the contribution of MM to LE with the highest loss (of 14 years in Denmark in 1971) (Figure 6.13). In contrast, the variation between females is much less among all countries and contributes about two years to the LE loss except for Denmark and England & Wales where the loss is unusually high and follows a pattern, which is usually typical for the male population.

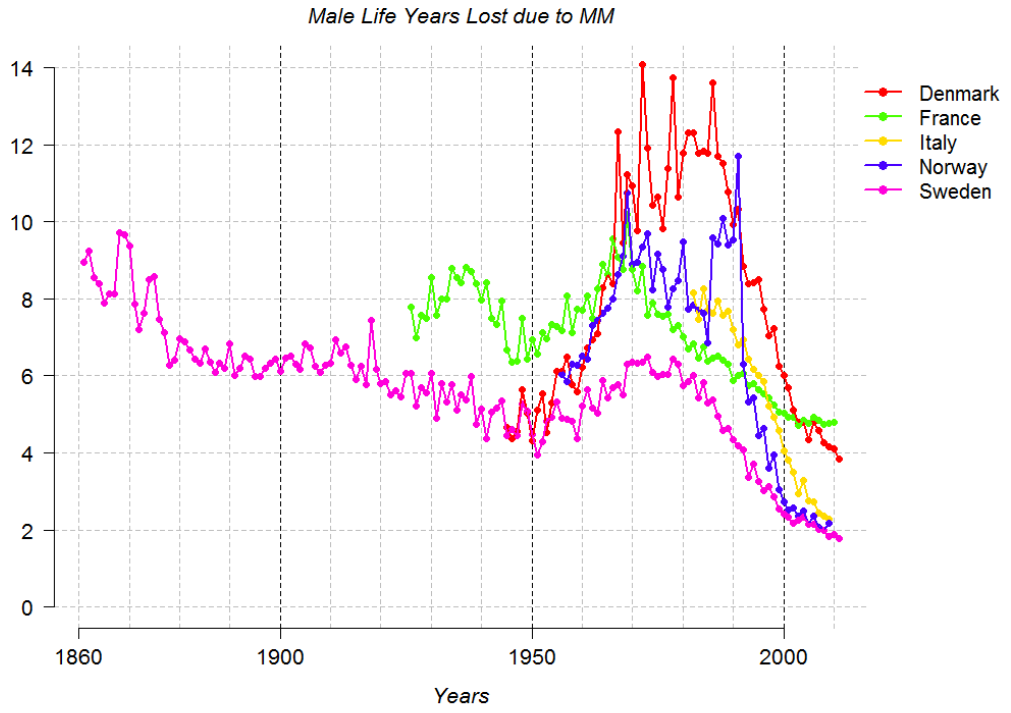

Figure 6.13. Life years lost at age 40 due to middle mortality (MM) for males in selected countries.

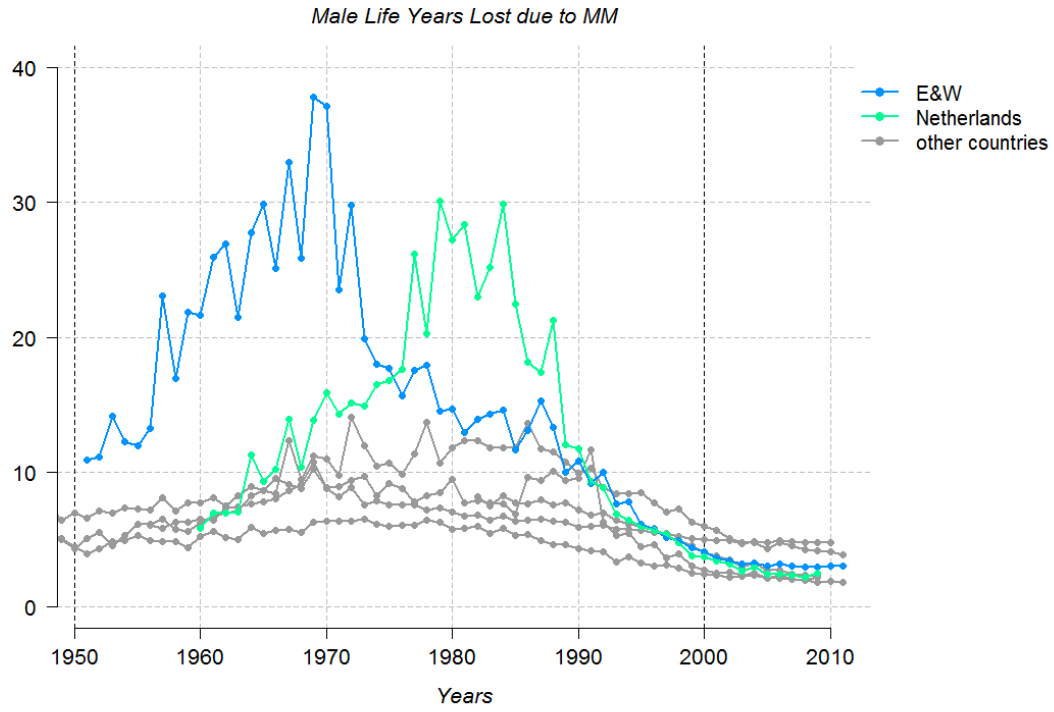

Figure 6.14. Life years lost at age 40 due to middle mortality (MM) for males in selected countries.

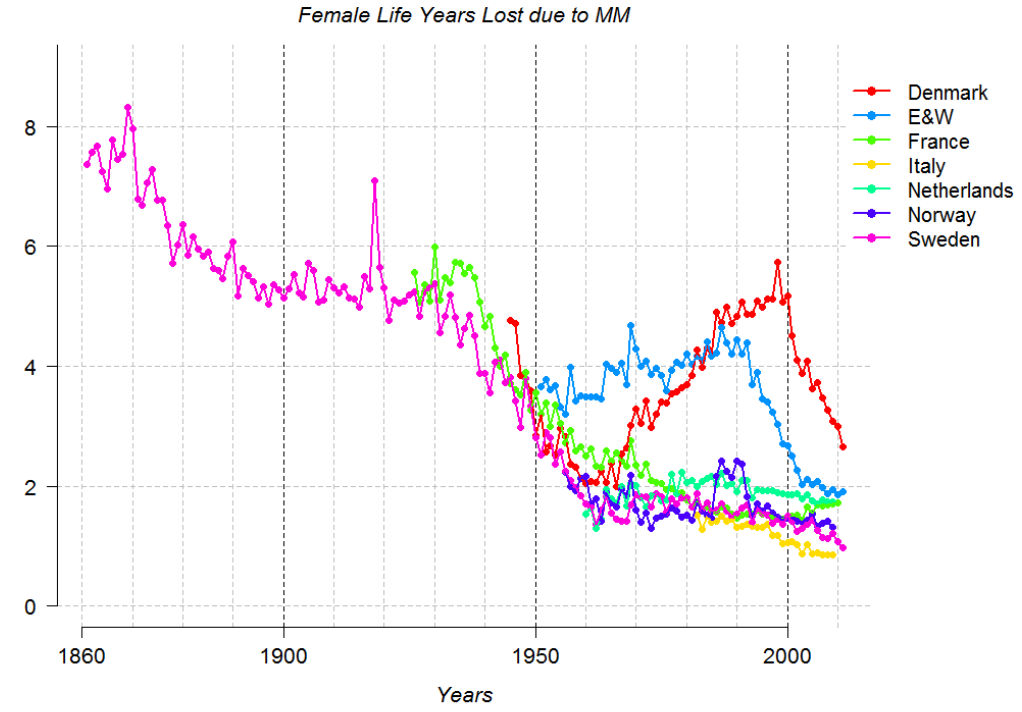

Figure 6.15. Life years lost at age 40 due to middle mortality (MM) for males in selected countries.

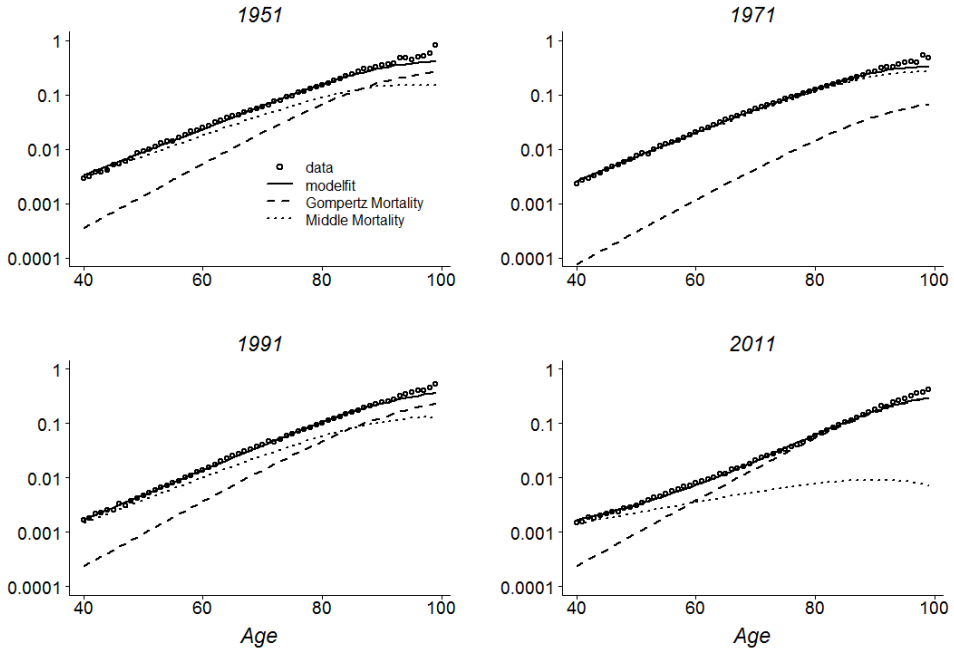

Figure 6.16. Male Mortality and model fit in England & Wales between ages 40 and 99. Middle Mortality is relatively high compared to senescent mortality.

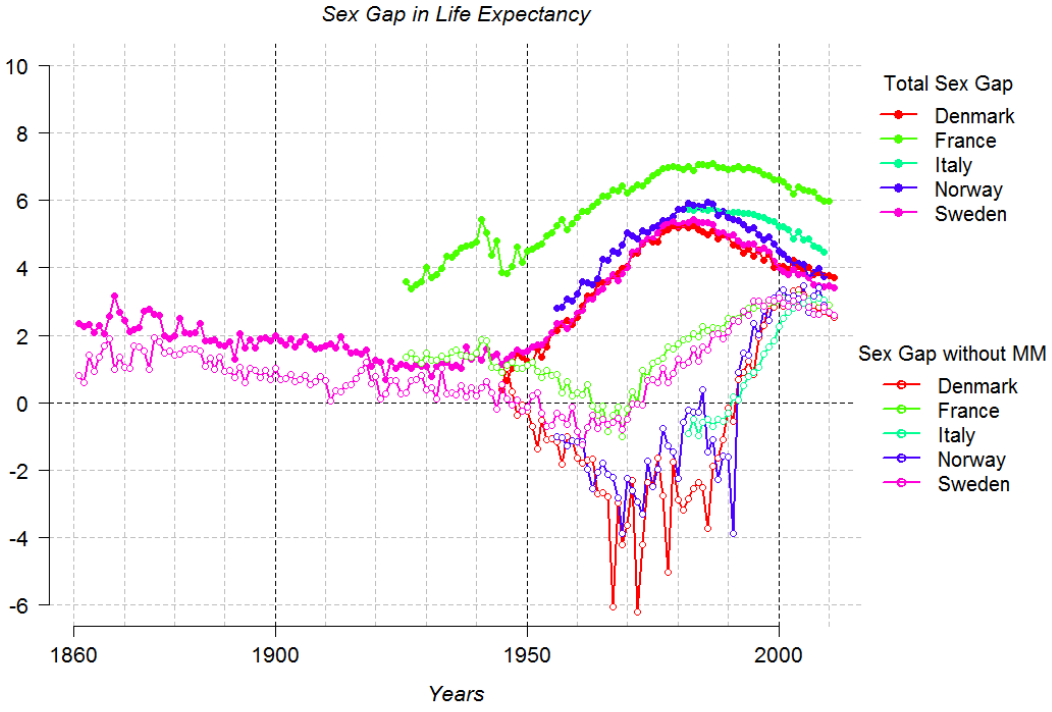

Figure 6.17. Female minus male LE at age 40 in terms of total mortality and senescent mortality (MM eliminated) due to middle mortality (MM) for males in selected countries.

The sex difference in LE in Sweden, as predicted by the κ-γ-Gompertz model, drops from around 2.5 years in the 1860s to a minimum of one year in the 1920s (Figure 6.17). After a gradual increase, the female LE is around 5 years higher in 1980 and drops down again to around 3 years of female advantage in 2011. If MM had been eliminated, the sex gap in Sweden would have been around one year in the nineteenth and early twentieth century and disappeared in 1950. In all countries the widening of the sex gap would have been delayed by up to two decades. MM thus accounts for up to seven years of the sex gap in the second half of the twentieth century. According to the κ-γ-Gompertz model, male LE would have been up to five years higher between the 1950s and the 1990s in Denmark and Norway, and still around 1 year higher in Sweden and France for several calendar years between 1950 and 1970.

6.4 Discussion

The first aim of the current study was to test whether *middle mortality* (MM) is an alternative model compared to the classic approach of a strict distinction between intrinsic and extrinsic mortality, which is realized in the mortality model suggested by William Makeham (1867). The log-ratio test indicates that the κ-γ-Gompertz model provides more information on the force of mortality compared to the γ-Gompertz-Makeham model (Figure 6.1), even though the latter is more parsimonious, since it has one parameter less. However, from a mechanistic point of view the κ-γ-Gompertz model provides a reasonable interpretation of MM, and the results support the idea that interactive risk factors shape adult human mortality trajectories. Even though there was no restriction in the slope of MM, it was found to be positive in all countries and periods tested in the study. The finding also addresses to the idea of interactive senescent and non-senescent forces proposed by others (e.g. Milne 2008). Whereas the intrinsic force reflects biological aging (*senescence*) and is probably constant over age and time, extrinsic forces have been interpreted here to stem from two types of risks. First, the interaction of a constant environmental risk with *senescence* is reflected by the classic Gompertz *law*. The second extrinsic risk type (or a sum of risks) has a varying age pattern. This risk

type interacts with *senescence* and results in a death distribution which follows a MM pattern.

In humans, it has been suggested that senescent forces are invariant over age and time (e.g. Vaupel 2010), whereas environmental forces account for the variation in human mortality as well as the sex gap (e.g. Rogers 2010). The incorporation of age-dependent environmental risk patterns in mortality models may provide a useful tool for testing a hypothesis about an invariant *rate of senescence* (ROS) or as to whether it differs between males and females, as suggested by some authors (e.g. Graves et al. 2006, Blagosklonny 2010, Crews 2003). Testing such a hypothesis falls outside the bounds of the current study, however, since the ROS is fixed to 0.14. More advanced methods in incorporating mortality progress and frailty are necessary to answer these questions.

Secondly, it was shown that MM accounts for a substantial part of LE loss, especially in males, and mainly accounts for the historical evolution of the sex gap in LE and mortality (Figures 6.6 to 6.11 and 6.12 to 6.17). The model also provides some remarkable insights into mortality dynamics in females and especially in males throughout the twentieth century. Actually, intercept parameters *a* (Gompertz) and *c* (MM) change almost parallel for both sexes in Sweden throughout the past 160 years (Figure 6.6). Whereas parameter *a* can be interpreted in terms of age-independent environmental risk factors, *c* reflects the level of age-varying environmental risk factors. As expected, both parameters are higher in males throughout almost all periods. An astonishing finding is that the sex difference in MM is mainly driven by the slope parameter of extrinsic risk factors (κ). This parameter accounts for the widening sex gap in life expectancy in the second half of the twentieth century (see Figure 4.2). Note that a lower κ leads to a high slope of MM and vice versa. If κ is behaviorally related, it follows that male behavioral risk declines slower over age compared to females. Late effects of behavior, such as cardiovascular diseases (CVD), lung cancer or liver cirrhosis, and direct effects of behavior, such as accidents and suicide, are the main contributors to the diverging sex gap since the 1950s (e.g. Waldron 1976, Wong et al. 2006). If the late effects of behavioral risk are relatively high, κ becomes small and the slope of MM increases. This is the case for males in Western countries between the 1950s and 1990s. In England & Wales CVD (Law and Wald 1999) and lung cancer mortality (Griffith

and Brock 2002) were especially high in males and may account for the distinctive mortality pattern. This probably explains the concave mortality pattern in England & Wales and the overestimation of the MM component between the 1950s and the 1970s. This also applies to the Netherlands and might actually be a problem of late effects of behavior during the 'smoking epidemic', the diverging sex gap in LE after the Second World War. For example, Pakin and Hrsinov (1984, see Chapter 5) stated that such a concave mortality pattern appears in several other Western countries. Another reason for the high trend of MM in other countries, for example in Denmark and Norway, might be partly due to competing risks. Competing risk was taken into account based on Chiang (1968, cited in Preston et al. 2001), but becomes unreliable, if mortality rates are too high (Preston 2001). This might be the case especially during the 'smoking epidemic', when CVD and lung cancer accounted for a widening sex gap in Western societies (Preston 1970, Pampel 2002, Retherford 1972).

Until the 1950s, κ was relatively high in both sexes. Hence, the slope of MM is relatively low, even though MM accounts for 5-10 years of LE lost. This is, because parameter *c* has more impact on MM. In Sweden *c* is relatively high until the 1950s, whereas the sex gap in LE is low (2 years). MM accounts for only one year of the sex gap, whereas the other year of the sex gap can be attributed to senescent mortality. A possible explanation for the historical trend of a small age increase of the MM component is that the individual was more exposed to uncontrollable hazards in the past, such as infectious diseases. Such diseases appear more evenly throughout the life course and can be treated more effective after the invention of antibiotics. In the past, the impact of such environmental hazards was therefore bigger and the Gompertz component possibly outcompeted MM at older age leading to a smaller slope in the non-Gompertz component. Also more non-behavioral but age-dependent extrinsic risk factors might have had a more important impact on middle age mortality. For example, viral infections affect especially young and middle adult age (Khiabanian et al. 2009) and may have played a key role in shaping MM in the past. Supporting this hypothesis is the increase of parameter *c* during the Spanish Flu in 1919-1920 in both sexes, whereas parameter *a* is not altered. Hence, the onset of MM is not necessarily behavioral driven, but may be affected by

influenza or other risk factors depending on the historical period and state of the epidemiological environment.

In the second half of the twentieth century the epidemiological transition continued with a rapid drop in infectious diseases (Omran 1971, Wolleswinkel-van den Bosch et al. 1997). In general, infectious diseases, such as inflammation, may be well described by the Gompertz parameter *a* in the model. The epidemiological transition is reflected in a gradual decline of *a* in females throughout the second half of the twentieth century, whereas parameter *a* almost stagnates in males between 1970 and 2000. Since parameter *a* becomes more important at old age, it might be that especially elderly men account for the stagnation. A likely explanation is that males use health services less often compared to women due to an over-estimation of self-reported health (see Chapter 2). Especially for elderly men this behavior has an important impact on survival. In this case, parameter *a* would also reflect a behavioral component, which leads to an age-independent risk factor. Given this, the widening sex gap since the 1970s may be partly explained by a slowing down or even a delay of the epidemiological transition in males.

6.5 Conclusion

The κ-γ-Gompertz model is a reasonable alternative to the classical γ-Gompertz-Makeham model, since it is based on the idea that mortality results from the interaction between extrinsic and intrinsic forces, rather than assuming a clear distinction between extrinsic and intrinsic mortality. This criterion is actually the strength of the model, making it far more realistic than former models of mortality. Moreover, the κ-γ-Gompertz model provides a better fit to the underlying mortality pattern compared to the γ-Gompertz-Makeham model. However, some causes of deaths are problematic and do not fit the age pattern of either the κ-γ-Gompertz or the γ-Gompertz-Makeham model. Hence, a future perspective would be to apply the κ-γ-Gompertz model to cause of death data with deaths due to delayed effects of behavior eliminated (such as several types of cancer or CVD). Another problem is that the model is still restricted by a high correlation between its parameters, which leads to instable parameter estimates for the complete model. Only if the Gompertz slope parameter *b* is fixed, does the model appear to be stable. Especially *b* is crucial

to estimate the *ROS*. Therefore, results for the MM component have to be interpreted carefully. Moreover, it might be that the *ROS* differs between males and females and, therefore, the impact of MM on the sex gap may be lower or higher compared to current findings. However, the accurate model fit indicates that a *b* value of 0.14 is a realistic assumption. More research is necessary to fully explore the unrestricted κ-γ-Gompertz model with more advanced estimation techniques.

Chapter 7

Final Discussion

This dissertation seeks to introduce a new approach in adult mortality modeling. Classic mortality models are based on a strict distinction between intrinsic and extrinsic mortality. Intrinsic mortality, which is expressed by an exponential function proposed by Gompertz (1825), is considered to reflect senescence (the process of physiological aging), extrinsic mortality reflects death due to all other causes after the age of maturity. The extrinsic part of mortality was first described by William Makeham (1867), who assumed an age-independent death rate to improve the fit of the Gompertz model. However, a more realistic interpretation of deaths incorporates the interaction of intrinsic and extrinsic risk factors. Based on this concept, the classification of mortality into extrinsic and intrinsic mortality components is not feasible. The concept of interactive risk factors presented here is an alternative idea that refuses the strict distinction between extrinsic and intrinsic mortality as it is often applied in demographic and biodemographic research (e.g. Finch 1994). The Gompertz model can be interpreted as the interaction of age-independent extrinsic risk factors with an increasing intrinsic risk, which is caused by decline in physiological function. Gompertz mortality applies to old age when external stressors are evenly distributed. However, extrinsic risk factors, which change over age and are not captured by the Gompertz model, may affect the shape of the mortality curve. This would possibly lead to an over- or underestimation of the Gompertz slope parameter and thus would weaken its explanatory strength in terms of the physiological rate of aging. In order to cope with this problem, a concept of interactive forces is emphasized. The mechanistic model, which is presented here, includes the middle mortality (MM) term as an alternative to the commonly used Makeham term. MM provides some mechanistic interpretation and integrates the interaction of physiological aging (intrinsic risk factors) and age-specific changes of extrinsic risk factors. One possible driving force of extrinsic risk factors is behavior. Several psychological and epidemiological studies indicate that risk-taking behavior declines over age. Moreover, several findings imply that mortality can be partitioned into a Gompertz and a non-Gompertz component (see

Chapter 5). In contrast to the classic concepts of a negligible small or constant mortality term at adult age, studies indicate that the non-Gompertz term increases approximately exponentially over age. A reasonable interpretation is that extrinsic risk factors decline over age and counteract senescence, which leads to a slower age increase of mortality compared to the Gompertz model. Therefore, in the present study a model was developed and tested which is based on the partition of all-cause mortality into MM and a Gompertz component. The model is tested by comparing two groups which differ in mortality due to higher risk-taking behavior in the shorter-lived group: males and females.

7.1 Sex gap in Mortality

Females live longer than males in virtually all populations (e.g. Glei 2005). The sex gap in LE has diverged throughout the twentieth century and was mainly caused by excess male behavioral risk (see Chapter 2). Therefore, the age pattern of high male mortality may provide important insights into the age pattern of MM. There are several studies which estimate the sex differential in mortality by means of the ratio. Here, however, the absolute difference has been chosen and computed for the following two reasons. First, the age pattern of the absolute difference between male and female mortality provides a reasonable approximation of MM, which is mainly driven by behavioral risk (see Chapter 2). Secondly, the difference is underreported in studies of the sex gap, even though it is often criticized (especially in medical research) to report on only one measure (e.g. King et al. 2012). The reason for this bias is that sex-specific risk factors are assumed to work in a proportional way. However, remarkable declines in mortality rates may be driven by risk factors which affect both sexes similarly. This would mean that the ratio is not only affected by changes in sex-specific risk factors, but also by changes in total mortality rates. A biased analysis of the proportional change in the sex gap could therefore lead to wrong conclusions.

7.2 Proportional versus Absolute Sex Gap in Mortality

The absolute sex differences in mortality provide a different picture than the ratio. However, a comparative analysis of both measures has not been performed so far. Depending on the measure employed, the evolution of the sex gap may be interpreted differently. For example, the ratio increased throughout the past 150 years in virtually all age groups especially during the twentieth century. In European countries in 2000, young adult male mortality was about three times higher than the corresponding female mortality. In contrast, the sex difference in mortality declined from 1860 to 2000 at middle adult age, but increased at old adult age. At young age, the difference was hump shaped in past periods, but relatively flat throughout the second half of the twentieth century. Hence, it is possible that the numerical property of either measure accounts for the trends, which are analyzed in Chapter 4.

Another finding is that the sex difference in mortality increases approximately exponentially over adult age. This pattern is stable across countries and over time (Chapter 3) and is one of the most important findings concerning the sex gap. Since female mortality is unlikely to exceed male mortality after age 50, it is also unlikely that men will ever outlive women at adult age in the developed countries in the future, even though the sex gap in LE has narrowed in the past decades. A consequence of this finding is that the masculinity ratio (number of men compared to women living in a population) will probably increase in Western populations. Even though there is a recent narrowing trend of the masculinity ratio (Avramov and Maskova 2003) due to faster improvements in male LE and a delay for female LE (Rostron and Wilmoth 2011), this trend might change with improving living conditions in the future.

However, there are a few exceptions in the past where female mortality exceeds male mortality at post-menopausal ages. Historical data on a period dimension show occasionally high female mortality after age 50, which might be due to poor data quality. Nonetheless, there are two remarkable examples of a stable and clear trend of high female mortality. French females born in the 1770s and the 1790s reveal a mortality disadvantage throughout their whole life span compared to males. This may be due to early life conditions characterized by famines in eighteenth century France. Early life conditions, though, have a weak impact on

adult mortality (Roseboom et al. 2001, Myrskylä 2010). The reasons for excess female mortality in historical France remains unclear. The pattern, however, reveals that the sex gap may be more variable than previously thought. Hence, it needs further investigation in the future.

Apart from these exceptions, the exponential age pattern in the sex difference seems to be a universal characteristic of human populations. The pattern is possibly caused by differences in physiological aging. However, the slope of the mortality gap between the sexes varies across time and between populations, which implies involvement of extrinsic risk factors. It is therefore likely that interactive effects of extrinsic risk factors amplify biological sex differences. The absolute sex difference therefore provides a possible age pattern of middle mortality.

7.3 The sex gap as a function of mortality levels

It is easy to overlook the fact that a proportional difference between two subgroups is not only a function of the different experience of underlying risk factors by each group, but also a consequence of the mortality regime of a population. This is due to a numerical artifact. Concerning the sex gap, the ratio of male to female mortality increases with a decline in the denominator. The remarkable decline in mortality rates combined with the remarkable increase in the sex ratio in mortality rates is suspected to be, at least partly, due to the numerical property. Since the absolute difference is positively associated with mortality rates, both measures, relative and absolute, have some characteristics, which weaken their explanatory strength.

An illustration is provided in Chapter 4 showing that the numerical property might lead to different interpretations of changing sex-specific risk factors of the ratio and the difference. The problem appears when populations are compared, which drastically differ in overall mortality levels. As demonstrated, the declining mortality level in westernized countries accounts for a substantial increase of the sex ratio of mortality rates in Western European countries. Especially at young age (18-39), the change in mortality explains around 90% of the change of the ratio and still between 78-95% of the difference during the ‘smoking epidemic’ (ca. 1950s until late twentieth century). Hence, the widening sex gap at young age during the

‘smoking epidemic’ is unlikely to be due to underlying sex-specific risk factors, but due to an improvement in living conditions and declining mortality rates in both sexes.

However, the widening sex gap is not only a numerical artifact. The study indicates that middle and old adult age groups experience a diverging sex gap, which cannot be explained by changing mortality regimes. This finding is in accordance with other studies showing that the diverging sex gap in the second half of the twentieth century is mainly driven by middle to old adult age groups (e.g. Lopez 1984). Moreover, the difference is less associated with mortality levels compared to the ratio. This implies that sex-specific risk factors tend to change proportionally rather than additively, which is supported by other studies (e.g. Bobak 2003). However, the present study shows that there is some bias from changes in mortality rates, possibly driven by sex-unspecific risk factors. Moreover, for some time trends the difference seems to be more appropriate than the ratio, since the former is less affected by changes in total mortality. For these reasons, the interpretation of the measure is context specific and conclusions should be based on both a relative and an absolute sex differential. The numerical problem is more frequently discussed in other fields of research. For example, Clarke et al. (2002) showed that an absolute or a relative measure of health inequalities between countries can lead to opposite conclusions about health differentials. Such findings have important influence on policy making and should be considered more in studies of the sex gap in mortality.

7.4 Middle Mortality

Middle mortality (MM) represents a mechanistic interpretation of a part of the mortality curve and replaces the classic concept of extrinsic mortality (Chapter 5). Makeham mortality becomes a special case of MM if the slope of extrinsic risk factors outweighs physiological aging. The most important finding here is that the κ-γ-Gompertz model, which incorporates MM, is a more appropriate description of mortality than the γ-Gompertz-Makeham model (Chapter 6). The result implies that MM is not constant or negligibly small, but contributes substantially to mortality still at middle and even old adult age. In terms of mortality projections, the dynamics of MM should be taken into account. It was shown that MM accounts for

approximately 4 to 10 years of LE loss after age 40 in the Swedish and French population before 1950 (Chapter 6). Whereas the importance of MM declined for females throughout the second half of the twentieth century, accounting for slightly less than two years, males suffered from high LE losses. In Denmark males would have gained up to a maximum of 14 years in LE in the second half of the twentieth century, if MM would have been eliminated. A possible reason for high MM in Denmark is that the country has suffered from unconventionally high mortality rates compared to other European countries during the second half of the twentieth century, mainly caused by high lung cancer and CVD mortality rates (Juel et al. 2000). Swedish males, who suffered the lowest impact of MM, still would have lived 6 years longer in 1970.

Moreover, the MM component accounts for large parts of the widening sex gap after 1950, whereas it accounts for only half of the sex gap in LE (~ 1 year) before 1950. The dramatic stagnation after World War II, which is commonly known as the 'smoking epidemic', is mainly due to an increase in male MM. In contrast, MM in females continued to decline, except for in Denmark and England & Wales, were a stagnating trend can be observed. The results imply that male MM is the driving force of the widening and the cross-country variation of the sex gap. This may be attributed to high rates of cardiovascular diseases (CVD), which vary more among males across countries (Thom et al. 1985) and account for the widening sex gap in LE (Lawlor et al. 2001, Waldron 1976). In recent years, the sex gap in LE converged in Western societies, which is reflected in a reduction of male MM. This trend will probably continue in the future, but is unlikely to disappear, since the absolute difference in mortality increases over age, and this pattern seems to be very stable across countries (Chapter 3).

Given these results, MM may be driven not only by the direct consequence of risk-taking behavior, but also by delayed effects of such behavior. For instance, a direct consequence of reckless driving is fatal accidents. For such causes the model provides a meaningful explanation for its parameters; C reflects the level of behavioral risk and κ defines how fast behavioral risk declines over age. However, mortality is more complex. Parameter κ therefore reflects any age changes in extrinsic risk over age. According to several previous findings, the widening sex gap in LE is due to the increasing lung cancer risk caused by smoking and CVD due to

diet and stress for males as observed in Westernized countries (e.g. Zhang et al. 1995). Hence, it is likely that κ is affected by late effects of such behavior. This possibly explains the continued decline of κ and therefore the increase of the MM slope after 1950. If delayed behavioral risk factors are large, this may lead to a problem in model fitting. The concave mortality pattern, as observed in England & Wales and the Netherlands, is probably caused by high CVD levels (Juel et al. 2000), which lead to an overestimation of the MM component.

The κ-γ-Gompertz model is, however, just a model. It only describes parts of reality and therefore fails in some instances. For example, the male mortality pattern during the 'smoking epidemic' seems to be a challenging scenario for MM. There were extreme changes after the Second World War mediated by the abrupt improvement in living conditions, individual freedom and wealth. To exaggerate the cause behind the widening sex gap: It seems to be that males refuse the benefits of this developments, but embrace its drawbacks. The diseases of modern societies occur predominantly in males; and with the advent of motor vehicles, male mortality has been exaggerated relative to female mortality due to a higher male tendency toward aggressiveness and recklessness (e.g. Wilson and Daly 1985). With the increasing accessibility of meat after the Second World War, fat intake increased and caused higher CVD risk in males, but not in females (Takata et al. 2013). The sex difference in mortality due to animal fat intake has biological reasons and is connected to the body fat distribution in both sexes causing a protective effect against CVD in females (Karastergiou et al. 2012). This example of the delayed consequences of exaggerated biological risk factors in males is challenging for a model based on the direct interaction of behavior and biological aging.

An opportunity to estimate MM properly would be to use life tables in which these deaths caused by late effects of behavior are eliminated. Lung cancer mortality might be a candidate, since it is mainly a delayed effect of behavioral and environmental hazards (Danaei et al. 2005). This would probably improve the fit of the κ-γ-Gompertz model. Another possibility is to extend the κ-γ-Gompertz model by additional mortality patterns accounting for the effects of smoking and diet. The problem is that auxiliary information on causes of death data often is not accurate (e.g. Modelmog 1992). This is because death certificates can be biased by practitioner experience, the number of autopsies and the medical technology to

identify a specific cause of death. Traffic accident data may provide a possibility, since it clearly represents an indisputable cause of death. However, one would need information on the severity of car crashes in order to distinguish between *avoidable* and *unavoidable* deaths.

Another limit of the model is that it provides unstable estimates when all five parameters are allowed to vary. Even though the b and γ were fixed based on auxiliary information, it is still debated to what extent physiological aging differs between the sexes (e.g. Graves et al. 2006, Graves 2007, Blagosklonny 2010, Crews 2003). This study, due to model limitation cannot test such a hypothesis. More advanced methods incorporating mortality progress and frailty are necessary to develop a stable κ-γ-Gompertz model.

The present study could give a first estimate of MM and discussed the consequences of interactive risk factors for mortality modeling. The analysis is based on the assumption, that the biological difference between the sexes is marginal, which is far from being an exotic assumption. For example, Luy (2009) compared the life expectancy of a cloistered population. Monks and nuns share a relatively similar life style, which reduces male behavior risk factors to a minimum. Luy estimated the sex gap due to biological differences at a maximum of 1-2 years. This implies a small sex difference in physiological aging, which probably has only a marginal impact on the estimation of MM. However, sex differences in accidental deaths between monks and nuns remain. This is surprising, since the reproductive role hypothesis predicts risk-avoiding behavior for women in the mother role and risk-taking behavior for the male breadwinner role (e.g. Waldron 1983). Since monks and nuns share similar social roles, but males still behave more recklessly, biopsychological factors, driven by hormones, may determine sex differences in risk-taking behavior (Luy 2009). Actually, evolutionary theories predict that sex differences in mortality due to reckless male behavior are a consequence of sexual selection in humans (e.g. Kruger and Nesse 2006). Moreover, the decline in aggressiveness and recklessness over age, denoted by parameter κ in the MM component, could possibly be an evolved trait to reduce the mortality risk during parenthood and, hence, increase survival chances of the progeny.

7.5 Biodemographic outlook

For most of their history, humans have lived in small groups as hunter-gatherers in savannah-like environments. The last 8000 years since the Neolithic Revolution, when humans began to adopt a sedentism lifestyle, and the last 150 years since the Industrial Revolution, when living conditions improved due to medical developments, appear to be a relative short time span compared to the more than 100,000 years of living in small nomadic groups. Hence, modern humans are therefore still adapted to ancestral living conditions, even though the environment has substantially changed. Given this, behavioral patterns are adapted to solve situations which appear to be of central importance for survival and reproduction in a past environment (Tooby and Cosmides 1990). Hence, in order to explain sex differences in behavior and aggressiveness, evolutionary theories provide a strong explanatory framework (e.g. Kruger and Nesse 2006). The following section outlines how differences in mating strategies shape behavioral differences between males and females in general and especially in humans. Several predictions which arise from evolutionary theories could probably be tested with or explained by the κ-γ-Gompertz model, especially by the age pattern of MM.

Social behavior has evolved to increase inclusive fitness, which is defined as the relative frequency of an individual's own genetic copies in the current and the future population (Dawkins 2006, William D. Hamilton 1964). Sexual reproduction is a fundamental way to transfer genes into the next generation. Reproductive success depends on maximizing the number and survival chances of the offspring. Due to fundamental sex difference, males and females benefit differently in terms of fitness, depending on the allocation of investment in either quality or quantity of their offspring (Trivers 1972). Females produce a few big gametes and males many small gametes, a phenomenon called anisogamy. Hence, there is an overproduction of male gametes in a population with an even masculinity ratio. This leads to higher competition among males to get access to the limited resource of female gametes. Bateman (1948) showed in an experiment with *Drosophila* that anisogamy leads to higher variation in mating success among males compared to females. The term polygyny reflects the inequality of reproductive success within the male population compared to the female population. In a thought experiment, George Williams

(1966) demonstrated how Bateman's principle applies to sexual selection in mammals. Pregnancy and lactation causes a relative high female investment of time and resources into the quality of the offspring. Hence, females benefit from choosing high quality males and from direct investment in offspring. In contrast, males increase their fitness outcome by investing in mating effort instead of investing in parenting. Actually, relative parental investment of males and females and not the gamete size are the driving forces for sexual selection in mammals (Trivers 1972). Based on the high female investment, Williams concluded that mammalian species, such as humans, should predominantly evolve polygynous mating systems (Williams 1966). In a comparison of mammalian species, it was demonstrated that with increasing measures of polygyny males show higher body size and aggressiveness and lower life expectancy compared to females (Clutton-Brock & Isvaran 2007). Humans fit into this scheme by showing a sexual dimorphism in height, weight and strength (Alexander et al. 1979) as well as greater male aggression and competitiveness (Kruger and Nesse 2006). Even though monogamy is the predominant marital system in Westernized countries and even enforced by law, the majority of all societies worldwide (84%) are polygynous (Ember et al. 2007). Actually, men tend to be less selective in mate choice, misinterpret potential mating opportunities, and are more competitive and aggressive compared to females (Buss, 1999). Moreover, several studies imply that humans, just like other animals, adapt their behavior based on the social, cultural or ecological conditions (e.g. Chisholm 1993, Ellis et al. 2009, Nettle 2009). This plasticity has evolved to maximize fitness in a changing environment and might be able to explain certain gender roles as well as the variation of sex mortality differences across cultures (Kruger and Nesse 2006). For instance, Quinlan (2008) showed that human maternal care is a function of pathogen stress in the environment to maximize fitness in pre-industrial societies.

The behavioral component of MM could provide a tool to test predictions implied by sexual selection theory. First, if higher aggression in males is a universal trait, male MM should be higher in all cultures. This is the case for all populations analyzed in Chapter 6 of this study. However, the full range of human societies also includes hunter-gatherer societies, which are closer to the living conditions of pre-historical human populations. These societies are also unaffected by high rates of

CVD mortality and lung cancer, i.e. by diseases typical for modern societies. Several well-studied hunter-gatherer societies show higher male mortality rates after post-menopausal age (Blurton-Jones et al. 1992, Blurton-Jones 2011, Gurven et al. 2007, Hill and Hurtado 1996, Hill et al. 2007). Whether the sex differences in hunter-gatherers are due to sex differences in MM, as shown for contemporary populations, could be tested by the κ-γ-Gompertz model. Secondly, male risk-taking behavior is probably higher in male hunter-gatherers, since these societies show higher rates of polygyny compared to Western societies (Ember et al. 2007). The κ-γ-Gompertz model could also be a useful tool in testing this hypothesis. The model allows the disentangling of mortality, which is caused by behavior and mortality due to other age-unspecific environmental risks, such as general standards of living or pathogen stress. Given this, MM should account for a larger sex gap in LE in hunter-gatherer populations compared to modern societies.

Additionally, another testable hypothesis concern the extent of mortality due to behavioral risk at old age. This means that the relative number of married men at older age is lower in polygynious compared to monogamous populations. Since unmarried men have generally higher rates of behavioral related mortality (e.g. Grove 1973), because greater mating effort is associated with risky behavior in men (Archer 2006), the male risk-taking behavior at old age should be higher in polygynous compared to monogamous societies. Therefore, the decline of behavioral risk factors, which is reflected by parameter κ, should be smaller for males living in hunter-gatherer societies compared to those living in industrial countries.

Moreover, hunter-gatherer populations have a more than 200 times higher mortality risk at age of maturity compared to contemporary Western societies (Burger et al. 2012). Burger and colleagues (2012) explain the large differences in mortality with external risk factors, like sanitation, nutrition, and public health. However, they are surprised by the finding that the difference is greatest during age at maturity. One would rather expect a low sensitivity in mortality at young age when selection pressure is highest. This is, because mortality causes the highest fitness loss at age of maturity. Therefore, one would expect less variation in mortality at age of maturity (Burger et al. 2012). A possible explanation for this obviously contradiction could be the fact that the authors used mortality rates of

both sexes combined. Even though absolute sex differences in mortality are small in contemporary societies, they might be much larger in hunter-gatherers and total mortality may be therefore driven by male mortality risk. Hence, it could be that a relatively large part of mortality differences between modern societies and hunter-gatherers at middle adult ages is largely due to male MM. The advantage of the κ-γ-Gompertz model is that it not only estimates behavioral mortality, but takes the interaction with environmental risk factors into account. Hunter-gatherers are facing higher rates of parasites and infectious diseases. Behavioral risk might lead to amplified mortality in such environments, since injuries and wounds due to violence or accidents have more severe outcomes than in populations, which have access to medical services and antibiotics. If male hunter-gatherers express higher risky behavior than males in industrialized countries, this could be an explanation for the big difference in young age mortality. Parameters κ and C provide a quantitative tool to test such hypothesis.

7.6 Conclusion

In conclusion, the ability to disentangle behavioral, environmental and intrinsic risk factors may be the biggest strength of the κ-γ-Gompertz model. This allows the testing of predictions about the complex causation between different extrinsic risk factors and mortality in human populations. Large parts of the varying sex gap in mortality throughout the last century can be explained by MM and behavioral risk factors. Moreover, the model is useful for fields such as biodemography for which a mechanistic mortality model is imperative in testing predictions based on evolutionary theories. Even though the model is not capable of explaining every aspect of adult human mortality, it is a promising approach to provide a reasonable interpretation of the so called ‘extrinsic mortality’. This feature is certainly a motivation to improve and apply the κ-γ-Gompertz model in future research.

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Appendices

A. Mortality Plateau

In the following it is proven that the κ-γ-Gompertz and the γ-Gompertz frailty model approach a mortality plateau at very old age, which appears to be at b/γ. According to Vaupel and colleagues (1979), the general expression for mortality rates in a population with γ-distributed frailties among the individuals is expressed as

$$\bar{\boldsymbol{\mu}}(\boldsymbol{x}) = \frac{\boldsymbol{\mu}(\boldsymbol{x})}{\mathbf{1}+\boldsymbol{\gamma}\boldsymbol{H}(\boldsymbol{x})}. \qquad (A.1)$$

In respect to the κ-Gompertz model, the individual mortality hazard ($\mu(x)$) is the sum of the Gompertz (GM) and the middle mortality (MM) components:

$$\mu(x) = \mu_{GM}(x) + \mu_{MM}(x) = ae^{bx} + ce^{(b-\kappa)x}. \qquad (A.2)$$

The cumulative hazard ($H(x)$, of $\mu(x)$) in (A.2) is

$$H(x) = \int_0^x \mu(t)dt = \frac{a}{b}(e^{bx} - 1) + \frac{c}{(b-\kappa)}(e^{(b-\kappa)x} - 1). \qquad (A.3)$$

Including (A.3) in (A.1) gives

$$\begin{aligned} \bar{\mu}(x) &= \frac{ae^{bx}}{f(x)} + \frac{ce^{(b-\kappa)x}}{f(x)} = \bar{\mu}_{GM}(x) + \bar{\mu}_{MM}(x) \\ &= \frac{1}{a^{-1}e^{-bx}f(x)} + \frac{1}{c^{-1}e^{-(b-\kappa)x}f(x)} \\ &= \frac{1}{F(x)} + \frac{1}{G(x)} \end{aligned} \qquad (A.4)$$

with

$$f(x) = 1 + \gamma H(x) = 1 + \frac{\gamma a}{b}(e^{bx} - 1) + \frac{\gamma c}{(b-\kappa)}(e^{(b-\kappa)x} - 1). \qquad (A.5)$$

If we let $x \to \infty$ and $b > \kappa > 0$, $F(x)$ transforms to

$$\lim_{x\to\infty} F(x) = a^{-1}\lim_{x\to\infty} e^{-bx}[1+\frac{\gamma a}{b}(e^{bx}-1)+\frac{\gamma c}{(b-\kappa)}(e^{(b-\kappa)x}-1)] \quad (A.6)$$

$$= a^{-1}\lim_{x\to\infty} e^{-bx} + \frac{\gamma}{b} - \frac{\gamma}{b}\lim_{x\to\infty} e^{-bx}$$

$$+ \frac{\gamma c}{a(b-\kappa)}\lim_{x\to\infty} e^{-\kappa x} - \frac{\gamma c}{a(b-\kappa)}\lim_{x\to\infty} e^{-bx} = \frac{\gamma}{b}\ .$$

According to (A.4)

$$\lim_{x\to\infty} \bar{\mu}_{GM}(x) = \frac{b}{\gamma}. \quad (A.7)$$

For $x \to \infty$ and $b > \kappa > 0$, *G(x)* becomes

$$\lim_{x\to\infty} G(x) = c^{-1}\lim_{x\to\infty} e^{-(b-\kappa)x}[1+\frac{\gamma a}{b}(e^{bx}-1)+\frac{\gamma c}{(b-\kappa)}(e^{(b-\kappa)x}-1)] \quad (A.8)$$

$$= c^{-1}\lim_{x\to\infty} e^{-(b-\kappa)x} + \frac{\gamma a}{cb}\lim_{x\to\infty} e^{\kappa x} - \frac{\gamma a}{cb}\lim_{x\to\infty} e^{-(b-\kappa)x}$$

$$+ \frac{\gamma}{(b-\kappa)} - \frac{\gamma}{(b-\kappa)}\lim_{x\to\infty} e^{-(b-\kappa)x} = \infty\ .$$

According to (A.4)

$$\lim_{x\to\infty} \bar{\mu}_{MM}(x) = 0\ . \quad (A.9)$$

Combining (A.7) and (A.9) gives

$$\lim_{x\to\infty} \bar{\mu}(x) = \frac{b}{\gamma}. \quad (A.10)$$

Under the assumption that $b > \kappa > 0$, MM tends to 0 at old age. Therefore, the plateau of the κ-γ-Gompertz model (A.10) is equal to the plateau of the γ-Gompertz component (A.7).

B. Maximum Likelihood Estimation

Death events are assumed to be Poisson-distributed at each single age x for a given population at a given year. The Poisson distribution is a special case of the Binomial distribution. The Poisson distribution approximates the Binomial distribution if the expected probability for an event (π), is small and the given sample (n) is large. Since age specific mortality rates in a population are small, it can be assumed that *Poisson ~ Binomial* (for further detail see, e.g., Clarke and Cooke 1998). In general, the probability density function for the Poisson distribution gives the probability that the random variable X is equal to the observed events k:

$$\Pr(X = k) = f(x) = \lambda^k e^{-\lambda}(k!)^{-1}; k = 0,1,2 \ldots; \lambda > 0, \qquad (\text{B.1})$$

where λ is the expected value of the random variable X and is calculated as the product πn. According to equation (B.1), the expected number of deaths in a population($E\mu$), where E are the person years lived and μ is the mortality rate, is reflected by λ. The observed events k are the actual number of death counts D in a given population, so that (B.1) becomes

$$f(x) = E\mu^D e^{-E\mu}(D!)^{-1}. \qquad (\text{B.2})$$

To test an age specific model, a probability density function has to be constructed for each single age year x. In general, the probability density function for more than one independent observation is

$$f(x) = \prod_{i=1}^{n} f(x_i). \qquad (\text{B.3})$$

The joint probability density function with parameter space Θ is

$$f(x|\Theta) = \prod_{i=1}^{n} f(x_i|\Theta) \qquad (\text{B.4})$$

This is the probability which we would expect for the random variable within a certain parameter space with known values. The reversed function is the Likelihood (L) function, which is analog to the probability of an unknown parameter space Θ conditioned on the observed events:

$$L(\Theta|x) = \prod_{i=1}^{n} f(\Theta|x_i). \qquad (\text{B.5})$$

Its logarithm is defined as the log-Likelihood (*logL*) function, which is

$$logL(\Theta|x) = \sum_{i=1}^{n} f(\Theta|x_i). \qquad (B.6)$$

Combining (B.2) and (B.6) gives

$$logL(\Theta|x) = \sum_{i=1}^{n}[D(x_i)\log\big(E(x_i)\mu(\Theta|x_i)\big) - E(x_i)\mu(\Theta|x_i) - \log(D(x_i)!)]. \qquad (B.7)$$

Since *–log(D(x$_i$)!)* does not change the shape but only the amplitude of the *logL* surface, (B.7) simplifies to

$$logL(\Theta|x) \equiv \sum_{i=1}^{n}[D(x_i)\log\big(E(x_i)\mu(\Theta|x_i)\big) - E(x_i)\mu(\Theta|x_i)]. \qquad (B.8)$$

The *logL* function is maximized by assuming a κ-γ-Gompertz (C.1) shaped mortality rate with an unknown parameter space, so that

$$\hat{\Theta} = \max_{\Theta} logL(\Theta|x);\ (\Theta \ni a, b, \gamma, c, \kappa;\ \Theta > 0) \qquad (B.9)$$

C. Sensitivity Analysis I: Parameter Sensitivity of the κ-γ-Gompertz Model

The *κ-γ-Gompertz* model is defined as

$$\overline{\mu}(x,y) = \left(a(y)e^{b(y)x} + c(y)e^{(b(y)-\kappa(y))x}\right)\bar{s}(x,y-x)^{\gamma(y)} \qquad (C.1)$$

$$with\ \ a,b,\gamma,c,\kappa\ \geq 0$$

where $\overline{\mu}$ is the force of mortality at age *x* in year *y* and $\bar{s}$ is the survival of cohorts at age *x* born in year *y-x*. Model (C.1) is similar to the model used for the analysis in Chapter 6 with the exception that all parameters are unfixed. A fundamental problem of fitting models with several parameters is that they might appear to be very sensitive to starting values (e.g., Saltelli et al. 2000). A possible source of the problem is a correlation between the model parameters. To account for this problem, model (C.1) is tested for sensitivity by performing several Maximum Likelihood Estimations (MLE, see Appendix B) of 5^5 parameter combinations (Table C.1).

Table C.1. Schematic illustration of parameter value combinations

	Starting parameter combinations				
1	a_1	b_1	c_1	κ_1	γ_1
2	a_1	b_1	c_1	κ_1	γ_2
…	…	…	…	…	…
1563	a_3	b_3	c_3	κ_3	γ_3
…	…	…	…	…	…
3124	a_5	b_5	c_5	κ_5	γ_4
3125	a_5	b_5	c_5	κ_5	γ_5

Following starting parameter values are used:

a_1 = 0.05* μ(0), a_2 =0. 1625* μ(0), a_3 =0. 275* μ(0), a_4 =0.3875* μ(0), a_5 =0.5* μ(0)

b_1 = 0.12, b_2 = 0.13, b_3 = 0.14, b_4 = 0.15, b_5 = 0.16

c_1 = 0.8* μ(0), c_2 = 0. 85* μ(0), c_3 = 0. 9* μ(0), c_4 = 0.95* μ(0), c_5 = 1* μ(0)

κ_1 = 0.09, κ_2 = 0.1025, κ_3 = 0.115, κ_4 = 0.1275, κ_5 = 0.14,

γ_1 = 0.15, γ_2 = 0.175, γ_3 = 0.2, γ_4 = 0.225, γ_5 = 0.25,

with $\mu(0)$ = 0.000616657.

Optimization method

In a first step, a specific simulated-annealing (SA) algorithm is applied to find the global maximum of the *logL* function [equation (B.9)] (Belisle 1992). The SA algorithm is a method applied in global optimization problems. The SA algorithm performs a random walk along the multidimensional Likelihood surface in order to detect its global maximum. The advantage of this method is that it is less conservative in searching in the parameter space for the maximum *logL* value compared to classic more conservative approaches. Classic optimization functions are based on algorithms, which search in the neighborhood of the *logL* surface based on the starting values or the values of the previous iteration. The algorithm detects the higher value on the neighboring surface and uses it as a starting point for the next iteration. This process is repeated until there is no improvement in the *logL* maximization attainable anymore. Such conservative method works out very well in smooth *logL* surfaces without local maxima. A more complex model, such as the *κ-γ-Gompertz* model, returns a rough and complex *logL* surface with several local maxima. Hence, the conservative algorithm may get stuck in local maxima and fails to identify the global maximum of the *logL* function. In such a case, the SA algorithm has some desirable advantages.

Instead of continuously searching around the local area of the surface, the SA algorithm repeatedly jumps to a random point far from the neighborhood. This allows to escape from a local maximum and increases the chances of finding the global maximum. After a certain number of iterations (set to 10,000 in this study) the procedure stops and returns to the possible parameter estimates. However, due to the random process, the parameter estimates of two MLE performances based on the SA algorithm may differ. Therefore, a conservative optimization algorithm is

performed afterwards. A more robust optimization method, developed by Nelder and Mead (1965), is used with the outcome of the parameter estimates of the SA algorithm as starting parameters. This procedure has also been used for the MLEs in Chapter 6.

Given that the algorithm may stop at a local maximum depending on the starting parameters, each parameter combination of Table C.1 is used as a starting point to perform a total of 3125 optimization procedures. The probability density function of the Poisson distribution is constructed by using death and exposure (person years lived) between age 40 and 99 of French females who lived in 1990 (source: www.humanmortality.org).

First, the estimated parameter values and the maximum *logL* estimate for each starting parameter combination are shown. Second, the association between the parameter estimations is analyzed.

Parameter sensitivity

Figure C.1 shows the solutions of all MLE's performed for all starting parameter combination. Each parameter estimate is plotted against the maximum *logL* (*max-logL*) values from each optimization. The red line indicates the parameter estimate at the highest value among all MLE's. b and γ estimates are dispersed over a wide value range, whereas a, c and κ values appear to be more concentrated around the estimate with the highest *max-logL*. The results indicate that the identification of the *max-logL* for the κ-γ-Gompertz model is very sensitive to the starting positions on the *logL* surface. Especially b and γ values estimates appear to be more dispersed compared to a, c and κ.

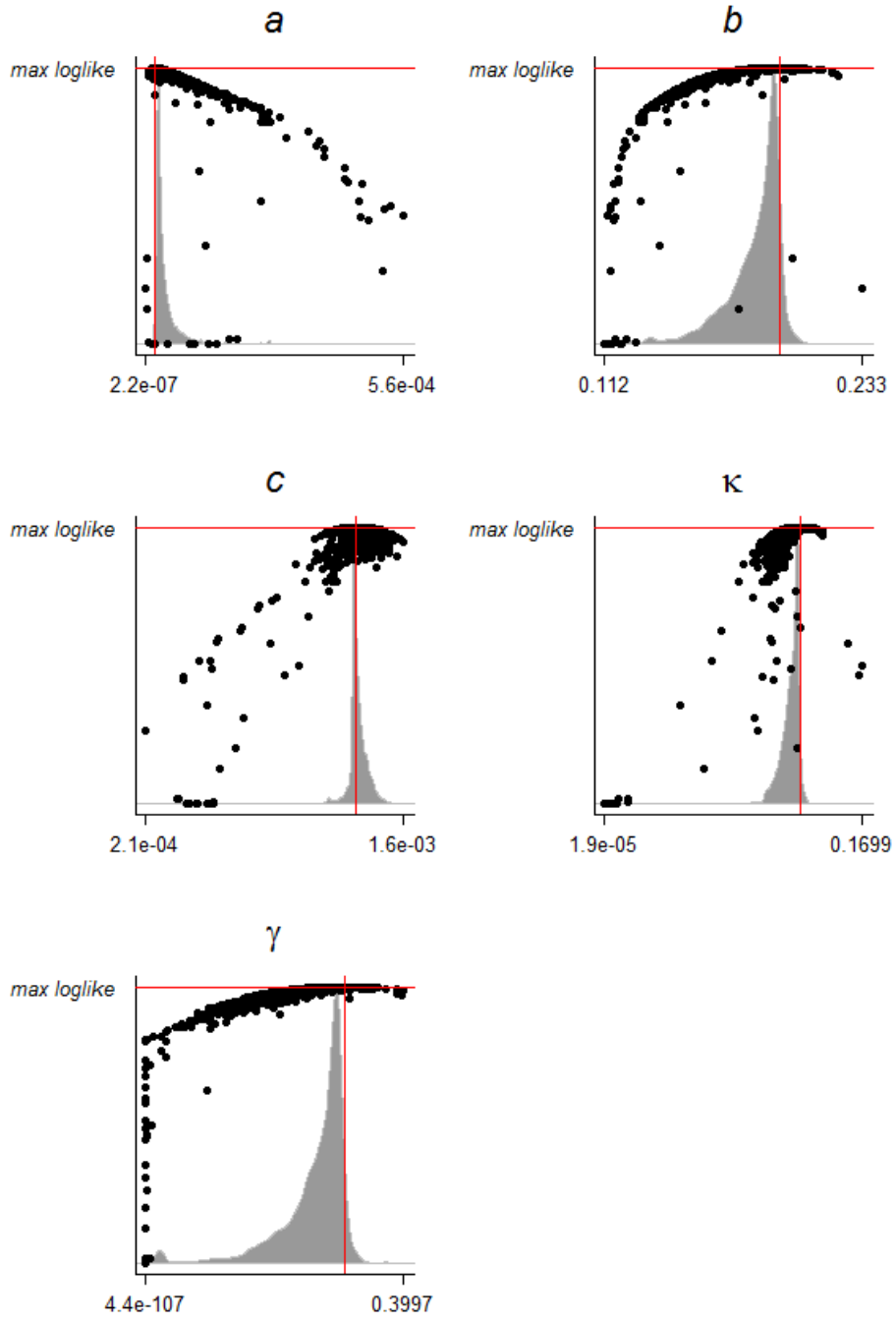

Figure C.1. Parameter estimates (x-axis) against max-logL values (y-axis) for the κ-γ-Gompertz model computed from 3125 different starting parameter combinations. Red lines indicate parameter estimates with highest max-logL Lowest and highest parameter values displayed on the y-axis. Gray area is the relative frequency of the parameter values constructed by computing Gaussian Kernel density estimates.

Parameter correlation

Figure C.2 shows that the association is very strong between parameters *a* and *b*. The negative exponential correlation between *a* and *b* is known as the Strehler-Mildvan correlation and is a property of the Gompertz equation (Strehler and Mildvan 1960). A second strong association exists between *b* and *γ*, which appears to be linear. This correlation likely accounts for the association between *a* and *γ*.

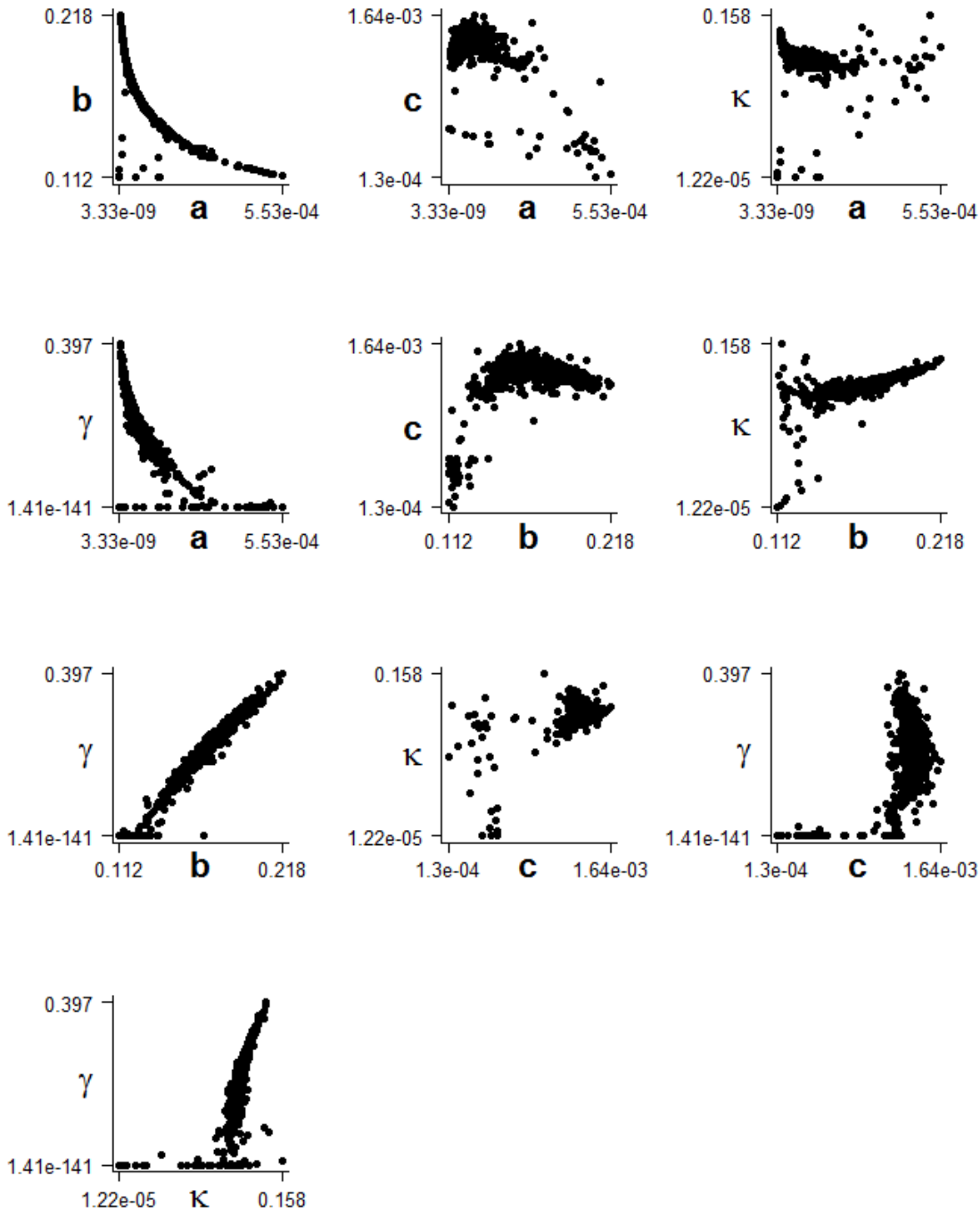

Figure C.2. Association between all parameter estimates of the κ-γ-Gompertz model for different starting parameter values.

Secondly, a sensitivity analysis of the κ-γ-Gompertz model (C.1) with fixed parameters b=0.14 and γ=0.2 is performed. This model is used for the computations in Chapter 6. The starting points for the MLEs have the same value range as in

Table 1. Instead of using 5 starting values for each parameter, 15 starting values are used. Each of the 15 starting values of parameters a, c and κ are combined, constructing 3375 possible parameter combinations.

Figure C.3 shows the estimated parameters computed by the MLEs. The distributions of the parameter estimates of the 3-parameter model are relatively dense compared to the 5-parameter model. The results show that the κ-γ-Gompertz model with a fixed b and a fixed γ value is stable. Based on these results, it was decided to use this approach in Chapter 6 to estimate the MM component.

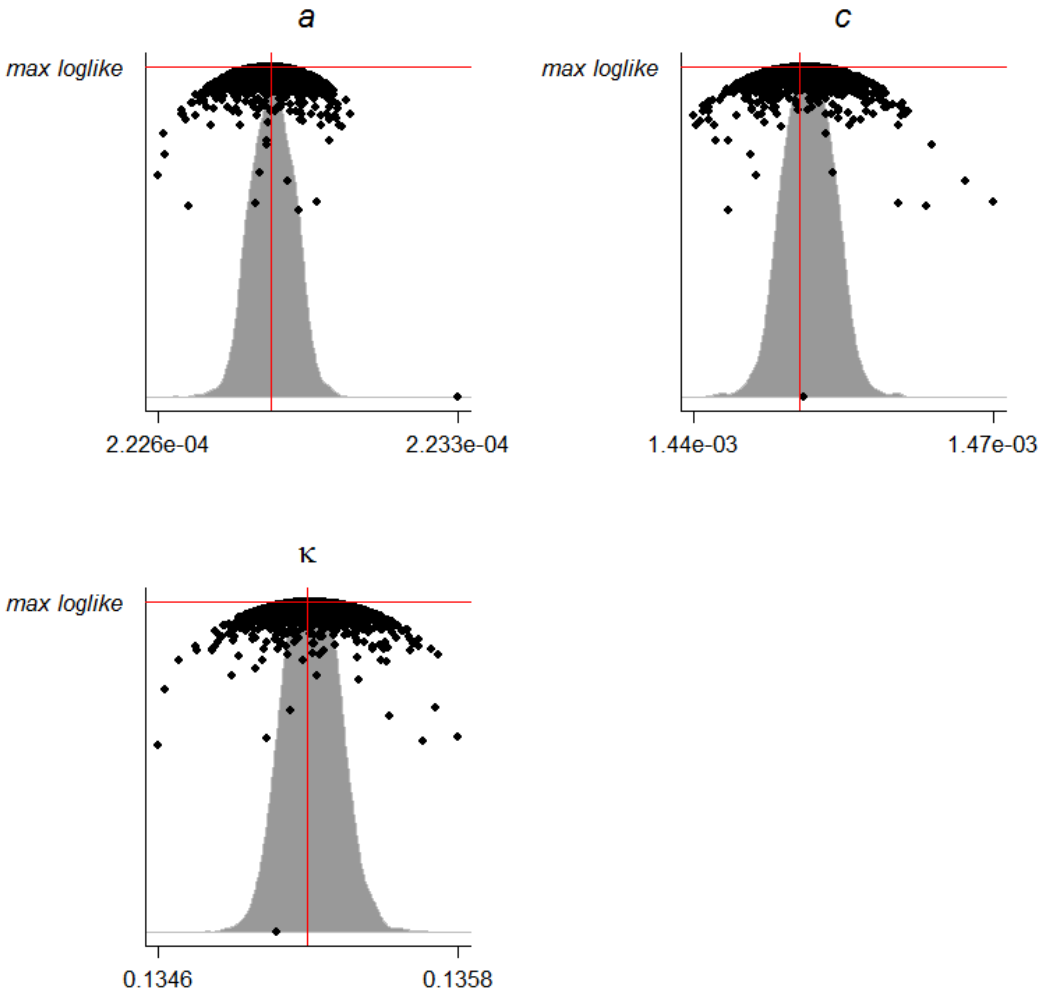

Figure C.3. Parameter estimates (x-axis) against max-logL values (y-axis) for the κ-γ-Gompertz model with fixed b=0.14 and γ=0.2, computed from 3375 different starting parameter combinations. Red lines indicate parameter estimates with highest logL. The lowest and highest parameter values are displayed on the y-axis. The gray area represents the relative frequency of the parameter values constructed by computing Gaussian Kernel density estimates.

D. Sensitivity Analysis II: Parameter b Variation and Life Expectancy

In Chapter 6, parameters *b* and *γ* of the κ-γ-Gompertz model are fixed. The decision, which values are chosen for b and γ, is based on the auxiliary information. The first information comes from Missov (2013), who estimated *b* at 0.14 for recent periods. The second piece of information comes from Gampe (2008), who estimated a mortality plateau in supercentenarians (age 110+) at approximately 0.7. Since the plateau can be expressed as *b/γ* (see Appendix A), a given *b* value allows to compute the respective *γ* value.

However, the analyses which lead to *b=0.14* and *γ=0.2* are debatable. First, Gampe (2008) used pooled cohort information of 637 certified supercentenarian individuals born in Europe and Northern America between 1852 and 1899. The plateau was estimated based on mortality rates of supercentenarians between age 110 and 114, since number of individuals become very low at higher ages. Therefore, confidence intervals, which were not calculated by Gampe (2008), may be very high and the real plateau could be slightly different from 0.7. If this is the case, this would affect parameters *b* and *γ*, too. Secondly, even though a reasonable value for *b* appears to be 0.14 (Missov 2013), there is still some uncertainty, because Missov fitted the γ-Gompertz model and probably faced fitting problems at old age accounting for unreliable *γ* estimates. Moreover, the author did not incorporate a non-Gompertz mortality component. Hence, uncertainty exists about the exact plateau and about the exact *b* value used in this study. Therefore, different parameters may have different impacts on the MM estimate.

Since *b* and *γ* are highly correlated (Appendix C), it is sufficient to fit the κ-γ-Gompertz model with varying fixed values in only one of these parameters. It appears to be more useful to try different values of *b*, instead of *γ*. This is, because *b* is more likely to affect directly the *κ* estimates, since the interaction of both parameters describe the slope of mortality. To account for effects of different *b* values on MM estimate, the κ-γ-Gompertz model is fitted with fix *b* values ranging from 0.13 to 0.16. The *γ* value is still fixed at 0.2 to account for the uncertainty of the mortality plateau. Given that the *b* values range from 0.13 to 0.16, the plateau ranges from 0.65 to 0.8. Data of 40-99 year old French male and females for the periods 1926 to 2012 are used.

Results

Figures D.1 and D.2 show the parameter estimates for different fixed *b* values for females and males, respectively. Parameter *a* is negatively affected by *b*. This correlation is also shown in Appendix C and described by Strehler and Mildvan (1960). Parameter *c* shows no change, or only a slightly negative association, with *b*, whereas κ is negatively affected by *b*. Especially in females κ is up to 0.04 higher when *b* is 0.13 compared to 0.16. The result also means that the slope in MM increases with increasing *b* value.

Figures D.3 and D.4 show the difference between the real life expectancy at age 40 and the life expectancy estimated by the κ-γ-Gompertz model with different fixed *b* values. The difference is smallest for *b* value of 0.14 in both sexes. After 1980 female life expectancy is slightly underestimated by the κ-γ-Gompertz model with a *b* value of 0.14. However, this concerns all *b* values. Hence, a *b* value of 0.14 provides the closest estimate of life expectancy in the majority of the periods.

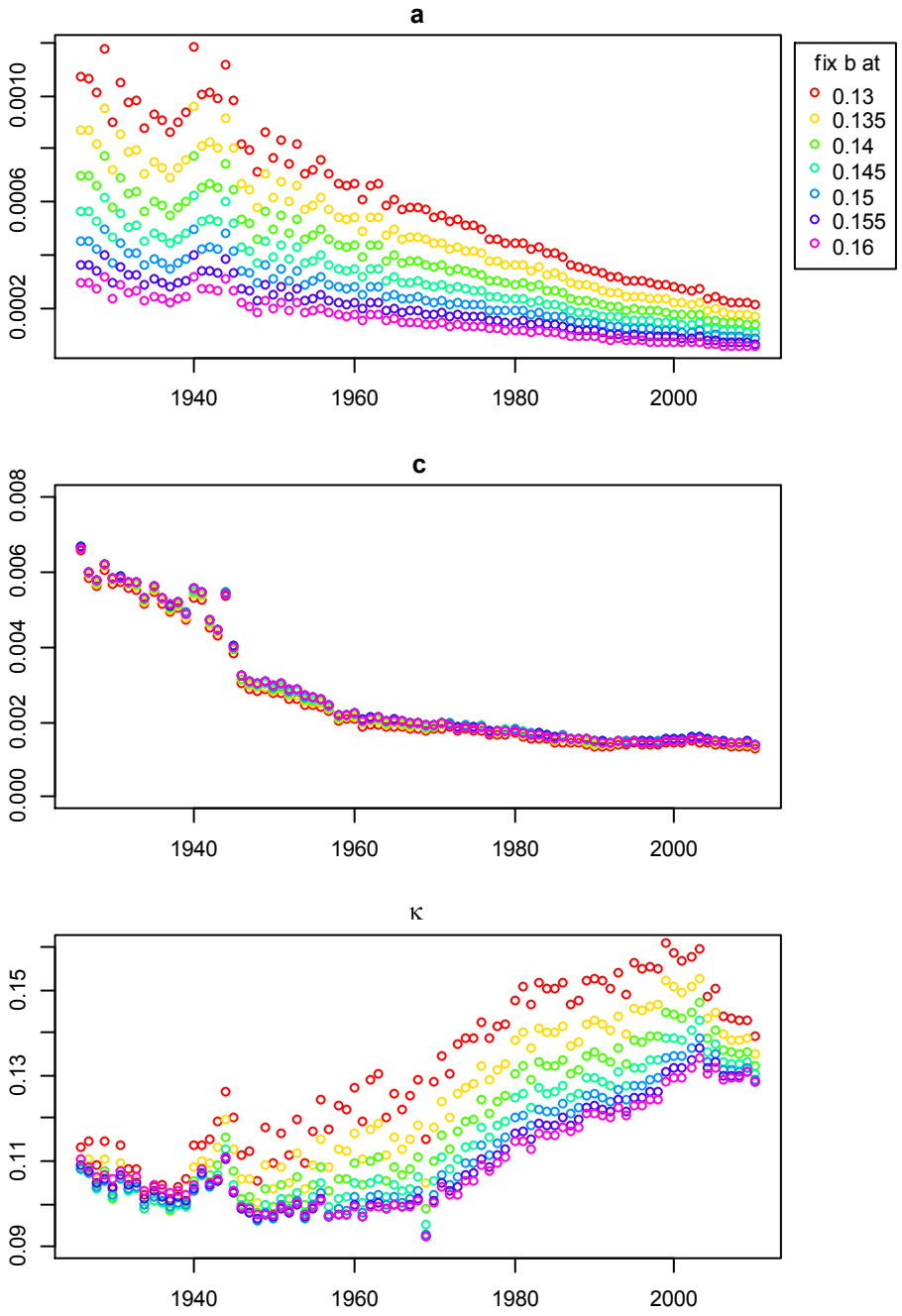

Figure D.1. Estimated parameters of the κ-γ-Gompertz model for French females 1926-2012.

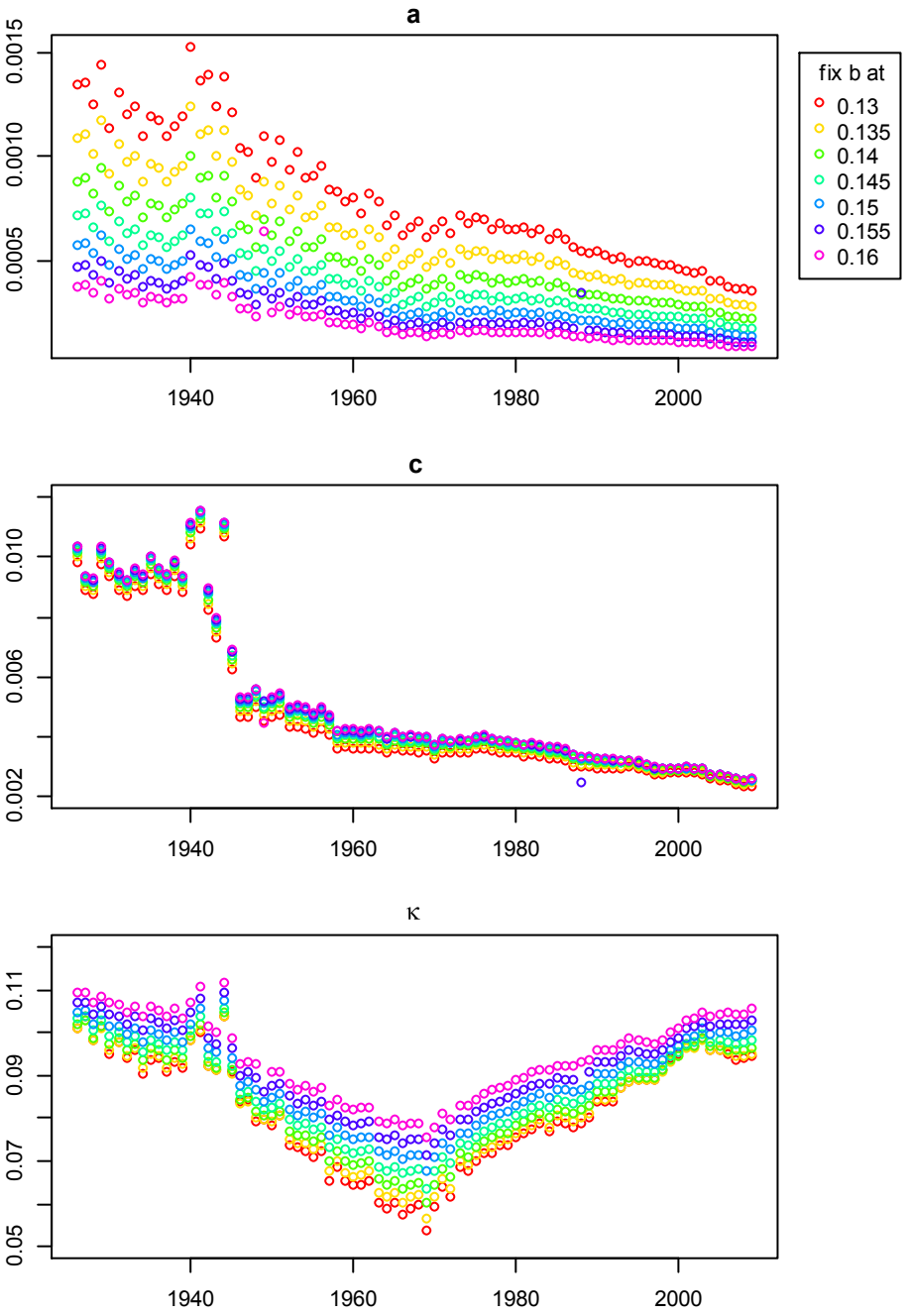

Figure D.2. Estimated parameters of the κ-γ-Gompertz model of French males between 1926-2012.

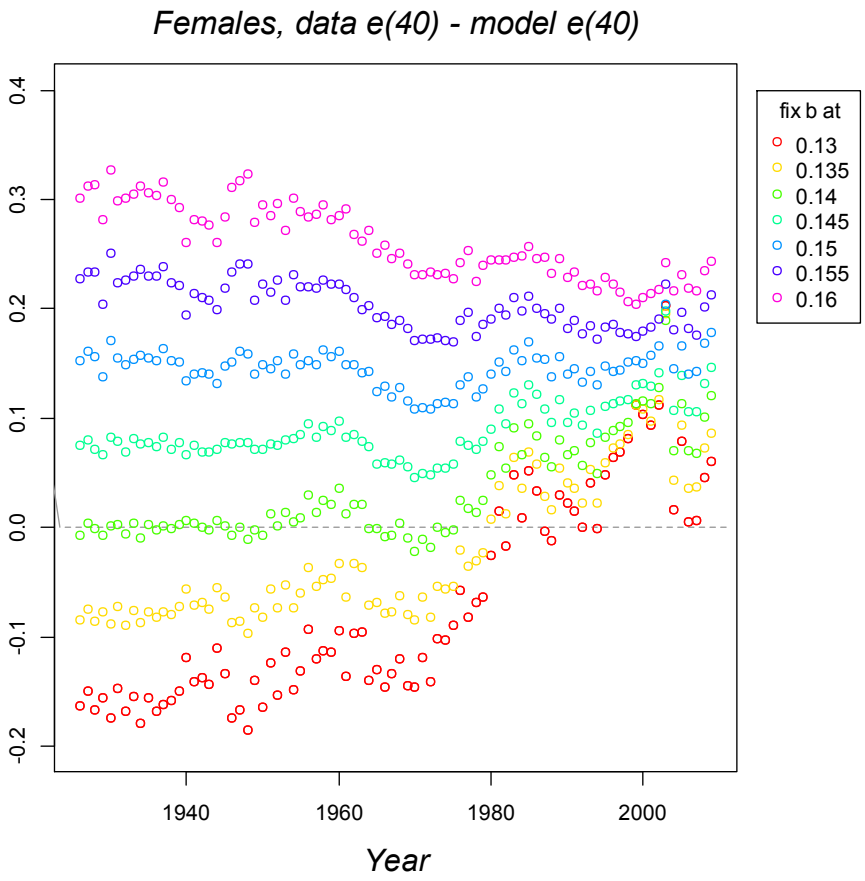

Figure D.3. Difference between life expectancy at age 40 from data and estimated by the κ-γ-Gompertz model with different b values of French females.

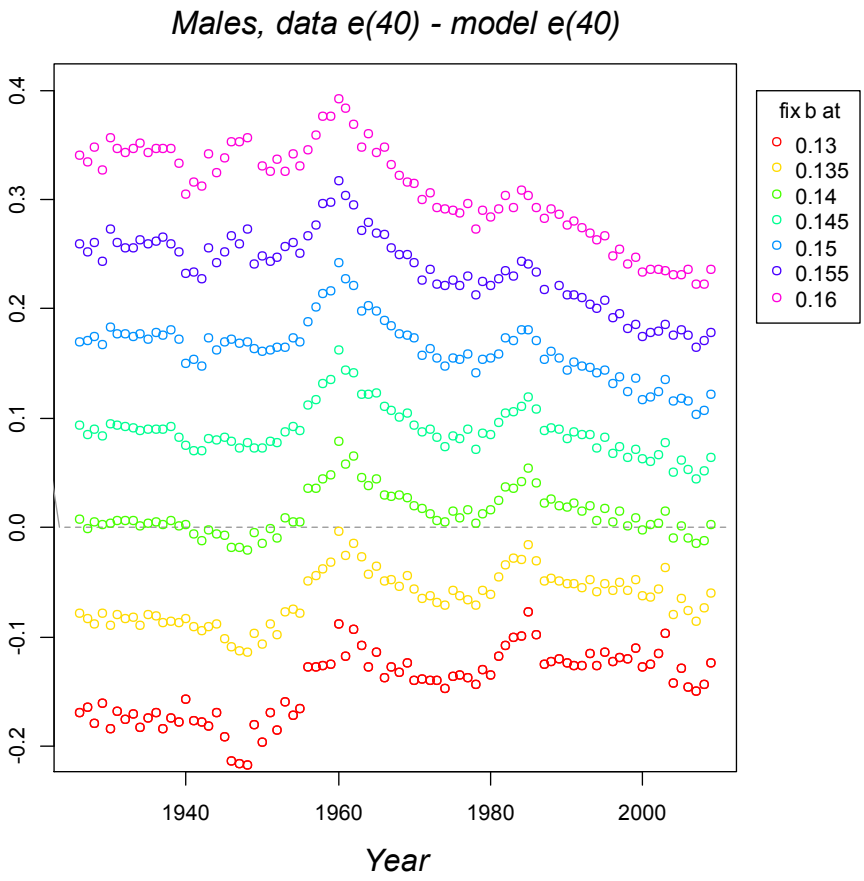

Figure D.4. Difference between life expectancy at age 40 from data and estimated by the κ-γ-Gompertz model with different b values of French males.

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Eidesstattliche Versicherung

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer Prüfungsbehörde zur Erlangung eines akademischen Grades vorgelegt.

Rostock, den 7. April 2015

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Oliver Wisser