Mortality Increase in Late-middle and Early-old Age: Heterogeneity in Death Process as A New Explanation

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Abstract

Deviations from the Gompertz law of exponential mortality increases in late-middle and early-old age are commonly neglected in overall mortality analyses. In this study, we first examined mortality increase patterns between age 40 to 85 from 16 low-mortality countries, and demonstrated sex differentials in these patterns which also change across period and cohort. These results suggest that the interaction between aging and death is more complicated than the Gompertz law had suggested and also challenge existing biodemographic hypotheses about the origin and mechanisms of sex differences in mortality. We then propose a two-mortality-process model that explains these patterns as the change in the composition of intrinsic and extrinsic death processes with age. We show that the age pattern of overall mortality and the population heterogeneity therein are possibly generated by multiple dynamics specified by the two-process mortality model instead of a uniform process throughout most adult ages. (Word Count: 147)

1. INTRODUCTION

The highly regulated yet complex age-specific pattern of overall mortality rate has long suggested a potential existence of a universal law in the mortality process (Olshansky and Carnes 1997). The most important finding in this field is arguably the Gompertz law, which shows an exponential rise in death rate between sexual maturity and old age (Gompertz 1825). However, systematic deviations from the log-linear trend observed in empirical mortality curves present great challenges to this law. Previous studies have paid great attention to one of such deviations, namely the old-age plateau, i.e., a leveling off of late life mortality (Carey and Liedo 1995; Horiuchi and Wilmoth 1998; Vaupel et al. 1998), but have not adequately addressed the deviations observed in other age spans (Milne 2007).

Among these deviations, the one in late-middle and early-old (50-70) age has been studied by several studies (Ekonomov, Rudd and Lomakin 1989; Himes, Preston and Condran 1994; Horiuchi 1983, 1997; Horiuchi and Coale 1990; Horiuchi and Wilmoth 1998; Milne 2007; Pakin and Hrisanov 1984). It is found that the rate of mortality increase in these ages become either faster or slower than the expected Gompertz exponential trajectory. However, the mechanisms that underlie this phenomenon remain unclear. This is primarily due to the complex patterns of the deviations that vary between the two sexes and across period: while females had consistent mortality acceleration at the age of 50-70 in all periods (Horiuchi 1997; Milne 2007; Pakin and Hrisanov 1984), their male counterparts in the same age-bands showed a greater diversity. In early periods, males had no notable acceleration and even exhibited a deceleration trend (Horiuchi and Wilmoth 1997; Pakin and Hrisanov 1984), but in more recent periods, their mortality pattern seemed to reverse and converge to that of females (Milne 2007).

While the old-age mortality plateaus stimulated a variety of theories in both demography and biodemography (Gavrilov and Gavrilova 1991, 2001; Mueller and Rose 1996; Vaupel, Manton and Stallard 1979; Yashin et al. 2001), these late-middle and early-old age mortality increase patterns should also be informative for generating or testing theories. The overall mortality patterns are observed from vital statistics based on national populations and thus are quite robust. The consistent deviations from the expected trajectory are not likely to be merely random fluctuations. Rather, they reflect certain underlying mechanisms of mortality beyond the extant understandings. Their sex-differential and time-varying characteristics open a unique avenue for selecting hypotheses that can incorporate time-changing dynamics associated with the differences between the two sexes.

In this study, we first explore the existing and potential hypotheses for such mortality increase patterns in late-middle and early-old age, conduct a thorough examination of these patterns from 16 low-mortality countries, and then propose and test our explanations based on a two-mortality-process model (Li and Anderson 2010; Li and Anderson 2012).

2. HYPOTHESES

Previous studies paid limited attention to the causes of the late-middle and early-old mortality increase patterns. Among the few exceptions, a first hypothesis considered these patterns as the continuation of an early-middle age (25-35) mortality acceleration, which is well recognized in the literature as the consequence of a constant background mortality (Makeham term) adding to the exponentially increased senescent mortality (Horiuchi and Wilmoth 1998; Makeham 1860). As the senescent mortality becomes dominated through aging (> age 40), the acceleration pattern should quickly diminish and the mortality trajectory ought to return to the Gompertz schedule around age 40. However, the mortality in later age exhibits either another round of acceleration

or deceleration; these patterns, therefore, cannot be attributed to the same reason as the early acceleration. Empirically, extant Gompertz-like models with a constant Makeham term still cannot precisely capture the mortality patterns in early-old age (Bongaarts 2005), which also serves as a piece of evidence against this first hypothesis.

A second notable hypothesis considered these later-life mortality deviations as the age change of sex hormone profiles. Based on the sex-differential patterns of males and females in the 1970s, it was hypothesized that the acceleration in female mortality was due to the loss of estrogen and hence loss of protection from various physiological disorders in post-reproductive ages (Horiuchi 1997). Compared to men who have a gradual decline in fecundity, the menopause of women would likely trigger abrupt acceleration in senescence, and consequently results in acceleration in mortality. Such hypothesis stems from the theory of evolutionary biology of aging (Horiuchi 1997; Kirkwood and Holliday 1979; Williams 1957) which considered the age-related increases in senescent or mortality as "a consequence of biological processes calibrated to the reproductive biology of a species"(Carnes, Olshansky and Grahn 1996). This theory provides a plausible explanation for the female mortality acceleration at post-menopausal age. Nevertheless, it fails to explain either the decelerating trends for male populations in early periods or the recent convergence in the patterns of males and females; in this sense, is inadequate to account for all the observed variations.

Given the convergence of the male and female patterns in recent years, a new hypothesis was proposed based on a concept of "repair senescence" (Horiuchi 2003), according to which the observed mortality acceleration is a result of changes in individual aging rate common for both sexes. Specifically, the rate of individual physiological deterioration (aging) is assumed to increase in early old age due to a decline in the rate of damage repair. To this end, the rate of

mortality increase, which is presumably associated with the pace of aging, accelerates. However, this hypothesis is still hampered by its ambiguity in explaining the sex and period variations of the acceleration patterns. In particular, a mathematical framework that can be used to quantify these differences is missing.

In light of these deficiencies, we propose an alternative explanation in this study. We argue that since the Gompertz law assumes senescent mortality is a uniform process throughout most adult ages, the violation to the law may suggest there are multiple processes that shape the senescent mortality patterns jointly. The age patterns of mortality increase, therefore, reflect the change in the composition of different mortality processes with age. We borrow insights from a recent model developed by Li and Anderson (2012), which partitions adult mortality into an intrinsic and an extrinsic process. In this model, the former process represents death from chronic damage accumulation and the latter one refers to death caused by acute forces that destroy the necessity for lives. Assuming both processes change with age, this two process framework provides a flexible structure to accommodate the changing dynamics of mortality and thus can possibly address the sex and period variations in the observed patterns. We will use this model to test our hypothesis that these late-middle and early-old mortality patterns can be attributed to the combination of multiple processes.

3. PATTERNS OF MORTALITY INCREASE IN LATE-MIDDLE AND EARLY-OLD AGE

A thorough exploration of the shape in mortality increase with age is crucial to the test of our hypothesis. In this regard, previous studies have several limitations. First, the early works were limited in period coverage and lacked the most recent data. As a result, they could not capture the changes in dynamics across historical time (Ekonomov et al. 1989; Himes et al. 1994;

Horiuchi 1983; Horiuchi and Coale 1990; Pakin and Hrisanov 1984). Second, although a recent study by Milne (2007) covered longer periods, its analysis relied upon a qualitative comparison of mortality shapes between two discrete age-bands rather than quantitative analysis of continuous measures of age change. Finally, all the works above were primarily based on period data and thus lacked a consideration of the cohort confounding effects. A growing body of literature suggests that cohort variations in smoking behavior, nutrition status, obesity level, among other risk factors, may produce notable differences between period and cohort patterns (Fogel 1994; Preston and Wang 2006; Yang 2008). Therefore, it is of great necessity to update both period and cohort age patterns of mortality increase to the most recent years.

Data and Methods

We used the data from the Human Mortality database (HMD 2010). The overall death rates of males and females are available in the HMD from age 0 to 110+ with one-year increment denoted as M_x, where x indicates single years of age. We selected both period and cohort data from 16 industrialized countries including Sweden, U.K., Italy, Japan, Netherlands, Spain, the U.S., France, Switzerland, Denmark, Australia, Canada, Belgium, Norway, Finland and Austria. For each country, six periods (1950-1959, 1960-1969, 1970-1979, 1980-1989, 1990-1999, 2000-2007/2008/2009) and four cohorts spanning a decade each (1880-1889, 1890-1899, 1900-1910 and 1910-1919), who had more complete data across adult ages, are examined. These samples cover most of the industrialized countries that have relatively reliable population mortality data. Note that we only use period data later than year 1950 when the background mortality is relatively small. By doing so, we attempt to minimize the effects of background mortality on the later life mortality patterns.

We examine the shape of mortality increase with age or the deviations from the Gompertz law by calculating the life table aging rate (LAR) which is defined as the percentage change in mortality rate at each age (Carey and Liedo 1995; Horiuchi and Coale 1990):

$$LAR(x) = \frac{1}{\mu(x)} \frac{d\mu(x)}{dx} = \frac{d \log \mu(x)}{dx} \quad (1)$$

where $\mu(x)$ is the force of mortality at exact age x. When mortality curves are fitted to a Gompertz model, $\mu(x) = aexp(bx)$, the LAR corresponds to the slope parameter b that is constant over age. Empirically, the LARs vary from age to age, suggesting deviations from the Gompertz law. For example, a decline of the LAR indicates mortality deceleration and an increase in LAR suggests mortality acceleration. The age pattern of the LARs is less frequently studied than that of mortality rates. However, the LAR can be more sensitive to the change of underlying dynamics of aging than the logarithm plot of mortality rates against age, because a nearly straight line of log death rates could have LARs that change substantially with age (Horiuchi and Coale 1990; Horiuchi et al. 2003).

The LAR can be estimated using discrete data of 1-year age-specific death rate by (Horiuchi and Coale 1990)

$$\hat{LAR}(x) = \left[\log M_x - \log M_{x-1}\right] / 1 = \log M_x - \log M_{x-1} \quad (2)$$

We smoothed the sequence of LAR by taking moving averages of seven successive values to reduce the stochastic variation in death rates. It should be noted that this method tends to "flatten original patterns to some extent by lowering peaks and raising troughs" (Horiuchi and Coale

1990), but as long as the observed trends are not driven by random processes, they should persist under the graduation procedure.

Results

The age patterns of the LARs from all 16 countries by time period are summarized in Fig. 1. For the purpose of this study, we only focus on the pattern between age 40 and age 85. The LARs are not constant with age as suggested by the Gompertz law. In fact, they vary in a range from 0.06 to 0.13 across countries and periods, implying that the death rate is rising at varying exponential rates between 6% and 13% per year of age.

Consistent with the observation from Horiuchi (1997), almost all female populations, except that in the U.K. in 1990s, exhibit a remarkable increase in the LARs around the ages of 50 to 70, indicating an acceleration of mortality increment in this age band. The pattern persists across all examined periods. Although the starting ages of increase in the LARs vary from population to population of females, there is a general tendency of increasing delays in those ages over time. In contrast, the male populations show much greater diversity across years. In the early period, i.e., from 1950s to 1970s, no significant increases in the LARs are observed in late-middle or older ages, but there are early increases that continue up to age 50 for many male populations. Following the rise, the LARs tend to either stabilize (Sweden, Japan, Spain and Norway) or show a considerable decline (all other countries) corresponding to mortality decelerations reported in early studies (Himes et al. 1994; Milne 2007). Starting from the 1980s, several male populations such as those of France and Japan begin to show a late-life increase in the LARs. When it comes to the most current period, the 2000s, all male populations show some increases in the LARs at similar ages with females. Significant rises in the LARs are found for 9

out of 16 countries including Sweden, Switzerland, France, Japan, Spain, Belgium, Norway, Finland and Austria, whereas the other countries show moderate rises.

[Figure 1 about here]

The age patterns in the LARs across six periods suggest that the acceleration of mortality in late-middle and early-old age does persist for females across time, but the pattern also becomes more and more apparent in male populations. While previous studies attributed the postmenopausal female mortality acceleration to the effects of fecundity declines and the loss of estrogen (Horiuchi 1997; Milne 2007), the recent disappearance of the sex differences in the patterns suggests alternative mechanisms at work. Also, the male mortality deceleration after an early acceleration in the early period, that is not entirely consistent with the "repair senescence" hypothesis common to both sexes, deserves additional attention. It should be noted that the above observations are based on period data only. We now present the cohort patterns of age changes in the LARs in Fig. 2.

For early cohorts, the two sexes show a surprisingly similar rise in the LARs in middle age even prior to the menopause age. But for more recent cohorts, males exhibit a more significant and earlier "hump" in the LAR pattern compared to females, i.e., first rise and then decline. The cohort patterns are complex, because they are also coupled with period effects which changed much more dramatically in the examined populations (Horiuchi et al. 2003). However, the pattern of rises in the LARs in middle or older ages for both sexes generally holds and even occurs simultaneously for nearly all early cohorts (born in 1880-1900). Therefore, the patterns of mortality increase, especially the acceleration, are not likely the consequence of pure cohort or period effects, but rather reflect common underlying dynamics of aging in both sexes.

[Figure 2 about here]

Neither the period or cohort patterns in the LARs between age 40 and 85 agree with the Gompertz law that the rate of mortality increase is invariant with age. And neither completely supports the estrogenic hypothesis that age patterns of fecundity decline and sex hormone profiles are the major causes for the sex differences in the age patterns of the LARs. Also, the "repair senescence" hypothesis alone is insufficient to explain the diversity of the observed LAR patterns. Two questions arise: 1).What is the fundamental cause for the patterns of mortality increase in late-middle and early-old age? 2). Why do these patterns differ between the two sexes for some populations but tend to converge for others? Extant mortality theories could not well address these questions, possibly because many of them rest on a common assumption that mortality as well as its interaction with aging is a uniform process throughout the entire adulthood (Horiuchi et al. 2003). Here we present a two-process view of mortality that provides a new conceptual framework to better explain the observed patterns of mortality rise.

4. THE TWO-MORTALITY-PROCESS HYPOTHESIS

Previous studies based on the cause-of-death (COD) data have shown that while the middle-age mortality is dominated by acute and infectious diseases, many old-age mortality are related to the progressive declines or failures in various physiological functions (Carnes et al. 2006; Gessert, Elliott and Haller 2002, 2003; Horiuchi et al. 2003). As suggested by Horiuchi et al. (2003) and Gessert et al. (2003), these patterns imply that the processes that lead to death may be "fundamentally different" between the two life stages. The middle and early-old age patterns of mortality increase, therefore, are likely to be a phenomenon associated with the transition between the two stages. However, the boundary between the two types of death is rather blurred, since both mortality rates are increasing with age (Carnes et al. 2006; Carnes, Staats and Sonntag

2008). It is too arbitrary to consider the middle-age mortality as not senescence-related or purely determined by external factors, because the frailty to external stresses also likely depends on the aging-related internal stability. Instead of hinging on an ambiguous classification for the specific cause of death, we are more concerned about illustrating the different processes that lead to death and how they produce the overall mortality patterns.

The Two-Mortality-Process Model

A two-process Markov model developed by Li and Anderson (2010; 2012) made it possible to mathematically address the two adult mortality processes. The framework is based on the premise that an individual is born with a fixed amount of survival capacity, i.e. *vitality*, that is randomly depleted over life through degenerative processes. Death occurs with complete vitality depletion from either intrinsic damage accumulation or when a large discrete extrinsic challenge momentarily depletes the current store of vitality (Fig. 3). Following the convention (Carnes and Olshansky 1997; Carnes et al. 1996), the former one is called intrinsic mortality, $\mu_i(x)$, and the latter is called the extrinsic mortality, $\mu_e(x)$. The total mortality then is the combination of the two mortality sources.

The vitality process is represented as a Wiener process, stochastically declining with age towards an absorbing boundary, where intrinsic mortality occurs (Aalen and Gjessing 2001; Anderson 1992, 2000; Anderson et al. 2008; Li and Anderson 2009; Sacher and Trucco 1962). The process is mathematically specified by a mean vitality loss rate and a variation term to reflect the heterogeneity among population that evolves with age. The intrinsic mortality rate is then derived from the death time distribution, i.e., the distribution of first arrival time of the Wiener process (Fig. 3ⓘ) (in this case is the inverse Gaussian distribution). This process

summarizes the actions of many mechanisms together such as a gradual degeneration in various physiological functions (Shock 1957) and the accumulation of random damages due to free radicals (Harman 1956), RNA mistranscription (Wiegel, Beier and Brehme 1973), shortening of telomeres (Passos, Saretzki and Von Zglinicki 2007), etc., that eventually goes beyond the body's self-repair capabilities.

Meanwhile, the extrinsic death process is realized with a similar structure to the Strehler and Mildvan (SM) general theory of mortality and aging (Strehler and Mildvan 1960). Death occurs when the external challenge magnitudes exceed the remaining vitality (Fig.①). The occurrence of challenges is assumed to follow a random Poisson process and the distribution of challenge magnitudes is assumed to be exponential. The extrinsic mortality rate can be approximated by an exponential increase function with age as in the SM theory (See supplementary material for the model details). Through such an approximation, the extrinsic mortality rate is independent of the intrinsic one and the overall mortality can be mathematically represented as the sum of the two mortalities:

$$\mu(x) = \mu_i(x) + \mu_e(x) \tag{3}$$

Note that in the model specification, both types of mortality processes are aging-related but they illustrate different pathways to deaths. That is, while the extrinsic mortality involves an acute force that destroys the necessity for living like a "robbery" to life, the intrinsic mortality results from a chronic wearing out of the potential life which occurs as a biological destiny. The mathematical realization of this model is described elsewhere (Li and Anderson 2010; Li and Anderson 2012) and briefly summarized in the appendix to this article.

[Figure 3 about here]

The Explanation of the Mortality Increase Patterns

As shown in Fig. 4 and Fig. 5, the two-process model fits both period and cohort data from U.S. and Swedish populations remarkably well and significantly better than the Gompertz model, as indicated by the BICs (Table 1). In particular, the model is able to capture both acceleration and deceleration patterns in mortality rise. Here we include an age span from 40 up to 100 years to show the continuation of the patterns throughout life. The middle and older age mortality acceleration can be easily interpreted as the emergence of intrinsic mortality adding to the exponentially increasing extrinsic mortality rate. Derived from the Wiener Process with an absorption boundary (see supplementary), the intrinsic mortality has a concave shape with age. It increases as the gradual concentration of intrinsic deaths in late-middle and early-old age but the increase decelerates due to the effect of selective survival in later age. That is, like the heterogeneity theory (Vaupel et al. 1979), the Markov structure in vitality process ensures some frailer individuals die early and some stronger ones die late, which leads to the accumulation of more robust individuals in very old age and hence the leveling off of mortality, i.e., the mortality plateau (Aalen and Gjessing 2001; Li and Anderson 2009; Steinsaltz and Evans 2004, 2007; Weitz and Fraser 2001).

The total mortality as the sum of the two types of death first displays a convex shape when the intrinsic mortality emerges to dominate and then changes to a concave shape due to the selective survival in intrinsic mortality. Since the extrinsic mortality shape is assumed to be invariant in this model, the total mortality shape is primarily determined by the intrinsic mortality. Correspondingly, the LARs have bell shapes in middle and old age for all populations, but the starting and ending ages of the bell shape and the degree of the curvature depend on how intrinsic mortality progresses with age. Therefore, the sex and period differences in the intrinsic

process are keys to explain the different patterns of mortality increase between the two sexes and across periods. We will illustrate this in the next few paragraphs.

For period mortality data of U.S. males (Fig. 4), the intrinsic mortality is more spread-out in shape in 1970 than 2005. This means the intrinsic death appeared much earlier (age 40) and the population heterogeneity in intrinsic mortality was higher in 1970. This earlier exposure to intrinsic death for some males was possibly due to unhealthy lifestyles such as smoking and drinking that chronically damaged the body and intrigued an earlier internal process of wear and tear. In particular, the tobacco use epidemic has been considered as not only the major cause of the higher mortality among male populations in the 1970s (Preston and Wang 2006; Yang 2008), but also the primary factor that greatly differentiated the population then (Diderichsen 1990; Diderichsen and Hallqvist 1997; Vagero and Lundberg 1993). The heterogeneity of intrinsic mortality for males was high in 1970s, because the population consisted of a large proportion of male individuals who smoked and the rest who still lived a healthier lifestyle. This means that a considerable proportion of individuals died from intrinsic causes much earlier and the remaining population quickly became an assembly of robust ones and thus achieved the mortality plateau earlier.

Correspondingly, the U.S. male mortality acceleration starts as early as age 40 in 1970, associated with an early rise in the LARs. Nevertheless, the much higher burden in extrinsic mortality of males clouds the total mortality pattern, such that the percentage increase in total mortality is not as apparent as that of females. The mortality leveling off due to selective survival also occurs early. In terms of the LARs, the decline starts as early as age 55. The observed deceleration of total mortality in early-old age for some male populations (Fig. 1) actually reflects the left-shift of the old-age mortality plateau.

With the advancement of medical technology and the improvement of living standards, the extrinsic mortality for male population is further reduced while the intrinsic mortality is substantially delayed to older ages. Meanwhile, the intrinsic deaths become more concentrated in later ages because of a shrinking intrinsic heterogeneity. The compression of death could be attributable to the further removal of tobacco use in male populations as well as more equal benefits from medical advances. In effect, the overall mortality pattern is more sensitive to the variations in intrinsic mortality, such that the older age mortality acceleration pattern becomes visible in male populations as shown in year 2005. These changes also occurred in female populations, but because females already had relative low extrinsic mortality and a later appearing yet more concentrated intrinsic mortality in early periods, the old age acceleration pattern was evident as early as 1950s. The most significant change in female populations from the 1950s to 2000s is the right shift of the mode of the LARs corresponding to the delays of intrinsic mortality (Fig.4).

Fig. 5 demonstrates that the mortality increase patterns in cohort data can also be explained by the two-mortality-process model. We take the Swedish cohorts in 1885 and 1905 as representative examples. In cohort 1885, both males and females exhibit similar intrinsic mortality trajectories and thus yield similar age patterns in the LARs as shown in Fig. 2. The sex differentials only appear in more recent cohort, i.e. 1905. Similar to the period changes, females experienced a considerable delay in intrinsic deaths from cohort 1885 to 1905, as suggested by a right shift in the mode of the LARs. In contrast, the male cohort in 1905 shows a larger variation and earlier manifestation of intrinsic death than cohort 1885, possibly due to the tobacco epidemic. Therefore, the increasing age pattern or the bell shape of the male LARs shows up early in recent cohorts (Fig 2).

[Figures 4 and 5 about here]

In conclusion, the two-mortality process model can answer the two questions we raised earlier. 1) The cause of mortality increase acceleration in late-middle and early-old age is the appearance of intrinsic mortality that adds to the early predominant extrinsic mortality. The acceleration pattern is more evident in the populations who have lower degree of intrinsic heterogeneity, i.e., the intrinsic death time is more concentrated. 2) The sex, period and cohort variations of the patterns are due to the differences in the progression of intrinsic mortality with age. Specifically, the deceleration pattern in early old age for some male populations corresponds to a leveling off of mortality rate following the early acceleration. This left-shift of mortality plateau is attributable to early exposures to intrinsic death for some individuals in these populations.

5. DISCUSSION

Ever since the proposal of the Gompertz law, population researchers have become highly interested in exploring how aging and death happen and why they occur along predictable paths. This continuing interest has led to the emergence and refinement of the field of biodemography that aims to "use biological arguments to investigate demographic phenomena" (Olshansky and Carnes 1997). On the one hand, biological theories were developed to explain the observed demographic patterns. On the other hand, these patterns provide explicit criteria for testing biological hypotheses. As a prominent example of the evolution of this relatively young field of population research, the pattern of mortality increase with age has stimulated the development of multiple biodemographic theories in the literature and also generated intense debates (Carnes et al. 1996; Olshansky and Carnes 1997). While there is still no dominating theory with

unambiguous evidence that leads to a complete rejection of the Gompertz law, the systematic deviations from the law in empirical data can play an essential role in extending or revising the law, enriching the biological theories and generating new hypotheses (Gavrilov and Gavrilova 2001; Mueller and Rose 1996; Vaupel et al. 1979). The late-middle and early-old age mortality acceleration and the sex differences therein discussed in this work is one notable kind of consistent deviation that should no longer be neglected in future investigations, as it suggests important new insights into the interplay of aging and mortality dynamics that are beyond any current understanding based on the Gompertz law.

Change-of-Aging-Rate vs. Two-Mortality-Process Hypothesis

The major contribution of our work is a new explanation to the mortality acceleration pattern in late-middle and early-old age based on a two-mortality-process hypothesis. Although the dynamics behind this phenomenon has been the subject of much scholarly work in the past, (Horiuchi 1997, 2003; Horiuchi et al. 2003; Milne 2007), the focus was primarily on the individual aging rate. A common assumption in this body of research is that the interplay between aging and mortality is in a uniform mode, such that changes in the mortality increase pattern would be directly associated with changes in the aging rate. Various explanations along this line, such as changes of system repair capacity (Horiuchi 2003), may still be plausible. However, the lack of a mathematical framework largely limits the applications of these change-of-aging-rate hypotheses.

The two-mortality-process hypothesis we propose here leads to an alternative explanation that the age pattern of overall mortality is possibly generated by multiple dynamics instead of a uniform process throughout most adult ages. From this perspective, the mortality acceleration is considered as a phenomenon associated with changes in the composition of two mortality

processes with age. The observations from cause-of-death (COD) data provide some biological and gerontological evidence to such a hypothesis that the dominating causes of death change from acute and infectious diseases in middle age to chronic and degenerative diseases in old age (Carnes et al. 2006; Gessert et al. 2002, 2003; Horiuchi et al. 2003). Correspondingly, we apply a mathematically tractable model to characterize the two mortality processes. In essence, the ability of quantifying all the variations in the observed patterns makes the two-mortality-process hypothesis meaningful.

It is worth noting that an absorption boundary for the intrinsic process in the model does not necessarily lead to an upper limit for human longevity. Rather, the dynamics of intrinsic mortality is quite flexible and can be constantly modified by all kinds of factors including medical, social, behavioral, and so on. In fact, the right shift of the mode of the LARs or the onset of mortality acceleration for both sexes from 1950s to 2000s demonstrated earlier reflects the delay of intrinsic death at the population level. We do not intend to be involved in the debate on human longevity; however we suggest there might be a basic biological mortality schedule which meanwhile is elastic to more complex dynamic changes through time. This, we believe, is key to understanding the highly regulated yet ever changing mortality patterns such as the trends of mortality increase in late-middle and early-old age of particular interest to this study.

Sex Differences in Mortality

Another potential contribution of the two-mortality-process model is that it provides a new insight into the sex differences in mortality patterns. Although the biological and behavioral differences between males and females may not be the fundamental reason for the *mortality acceleration* in middle and early-old age, they may still play a major role in explaining the sex differences in *mortality levels*. The higher extrinsic mortality in males is likely associated with

less robust physiological function in resisting stress, more reckless behaviors and harsher working conditions (Crimmins and Finch 2006; Nathanson 1984; Owens 2002; Waldron 1983), all of which increase males' exposures and/or vulnerabilities to external challenges. Meanwhile, the less healthy lifestyles such as drinking and smoking and less protection from sex hormones of males contribute to both their higher extrinsic mortality and more progressive decline in the internal process and consequently earlier intrinsic deaths. In addition, more diverse health behaviors can contribute to a higher degree of heterogeneity in mortality in male populations

It is interesting to note that while sex differences in the extrinsic process are relatively persistent, the gaps in the intrinsic process have largely diminished in recent periods (fig. 4). Specifically, from 1970 to 2005, the male-to-female ratio of age-adjusted extrinsic mortality was only reduced by 5% (from 1.54 to 1.46), whereas that of intrinsic mortality dropped by almost 50% (from 2.38 to 1.29). The reduction in intrinsic mortality gap can be possibly attributed to the large cessation of smoking in males (Preston and Wang 2006; Wang and Preston 2009) and the associated decline in the population heterogeneity in intrinsic mortality (Li and Anderson 2012).

Implications for Mortality Projection

The two-mortality-process model can characterize the temporal dynamics of mortality change, which has important implications for predicting future mortality trends and longevity. Accurate forecasting stems from a precise description of past mortality trends (Bongaarts 2005) and a thorough understanding of the mechanisms that produced such trends. The projection of mortality pattern will be more than identifying the trends of the baseline mortality (Gompertz parameter *a*) and the slope of mortality change with age (Gompertz parameter *b*), but include further information about the curvature of mortality increase in old age, which is mostly determined by the intrinsic mortality process. The change of intrinsic mortality now becomes the

major force in longevity evolution and will affect future longevity most (Goldstein and Cassidy 2012). The evolution of the intrinsic mortality has two dimensions: the mean and the degree of variation in the death time. The past several decades (e.g.1970-2005) are featured with both a delay and a compression in intrinsic death. It will be interesting to see if both patterns will continue or if new features will emerge.

Furthermore, the intrinsic-extrinsic framework provides a unique way to explore the future sex gap in mortality. As the smoking patterns between males and females converge (Preston and Wang 2006), the intrinsic mortality ratio (male-to-female) is expected to continue dropping. However, whether the sex gap in mortality will disappear at all is still questionable. The higher extrinsic mortality rate of males are associated with their physiological vulnerability to external challenges (e.g. infection diseases) and higher risky behaviors (Owens 2002). These are mostly biologically and socially constructed and culturally conditioned characteristics of males in human societies and may not be completely eliminated. Consequently, the sex differences in extrinsic mortality are likely to maintain at a stable level. Meanwhile, since the intrinsic mortality reflects the physiological degeneration process that is common to both sexes, the sex gap in intrinsic mortality can be potentially further reduced. In this sense, the male and female mortality trajectories in old age, where intrinsic mortality plays important roles, may continue converging; while their mortality ratio in middle and early old age, where extrinsic mortality dominates, will likely persist in the future.

We will explore the details of how this framework can be used in mortality projection in future studies.

Overall Mortality vs. Cause-specific Mortality

Analyzing both overall and cause-specific mortality data have potential benefits for understanding the mortality dynamics, but the two types of data provide different perspectives in this regards. While the cause-specific mortality pattern can suggest some specific and direct biological pathways between disease and death, the overall mortality pattern tends to reveal general mechanisms that underlie the aging and mortality process.

In this study, we borrow insights from early cause-specific mortality studies and develop the two-mortality-process hypothesis based on the previous findings that the fundamental causes of death could be different between middle and very old ages (Carnes et al. 2006; Horiuchi et al. 2003). However, our analysis is exclusively focused on overall mortality and relies on a pure mathematical partition of mortality. In many ways, the two-mortality-process model is still an idealized construction that summarizes many specific mechanisms. It is, after all, difficult or impossible to capture all the complexity of the aging and mortality process. Also, when vitality is low in extremely old ages, the boundary between intrinsic and extrinsic mortality may be particularly blurred. While it is usually considered that death at very old age is the consequence of damage accumulation to critical conditions and should be classified as intrinsic mortality, physiological frailty at that time may also make individuals more vulnerable to exogenous shocks and challenges that lead to extrinsic death. We understand such limitations, but we still prefer a mathematically tractable mortality partition to the death classifications based on cause-specific data is because there are two major problems with using the COD data.

First, for some diseases such as cancer, the etiology and its interaction with biological factors and senescence are still not entirely clear. Although there is a strong age pattern of cancer mortality, it remains inconclusive how aging factors contribute to the development of cancer (Peto and Doll 1997). While some cancer deaths result from chronic development of

malignancies inside of the organism sharing similar pathways with aging, e.g. many cancers occurring at old age (Cutler and Semsei 1989), some other more acute cancer deaths are clearly attributed to exposures to strong external carcinogens, e.g. radiation-induced (Bast et al. 2000) or infection-related cancers (Anand et al. 2008), and have weak links to aging. It is difficult to synthesize general understandings from all the uncertainties of the disease mechanisms, particularly for those diseases with multiple pathways and involving both intrinsic and extrinsic factors.

Second, COD recorded from death certificates may not accurately reflect the actual causes, especially for the older adults who possibly died from the combined effects of several chronic conditions and maybe even environmental hazards that induce the ultimate death event. Inevitably, some of these conditions are omitted from death certificates, which lead to the systematic underreporting of disease-specific deaths (Gessert et al. 2003).

However, with improved knowledge in the etiology and identification of different causes of deaths, we believe future investigations of COD data can provide further and explicit empirical tests of the extrinsic and intrinsic mortality processes and contribute to the understanding of the general process of mortality as well as the interaction between aging and death.

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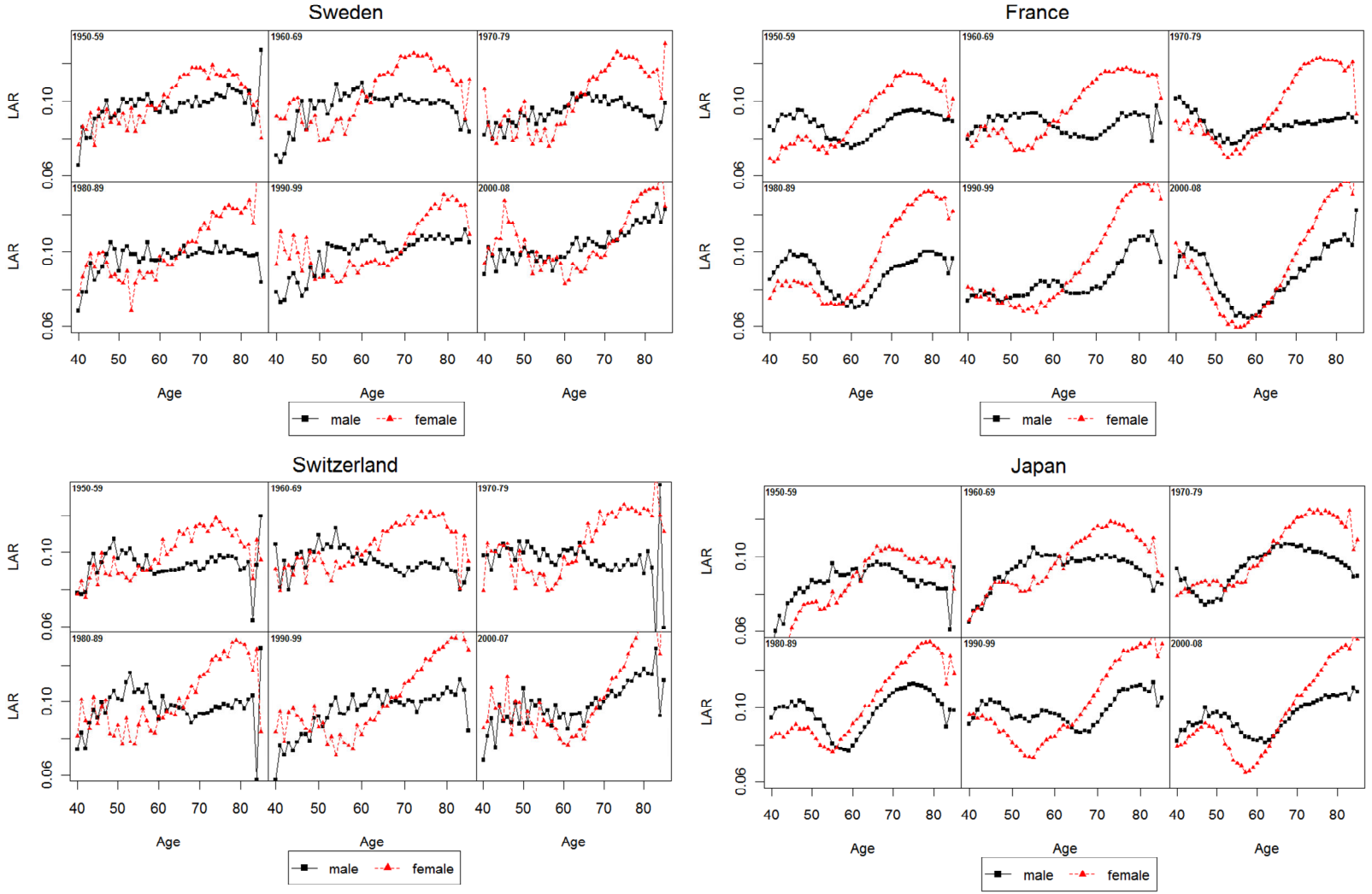
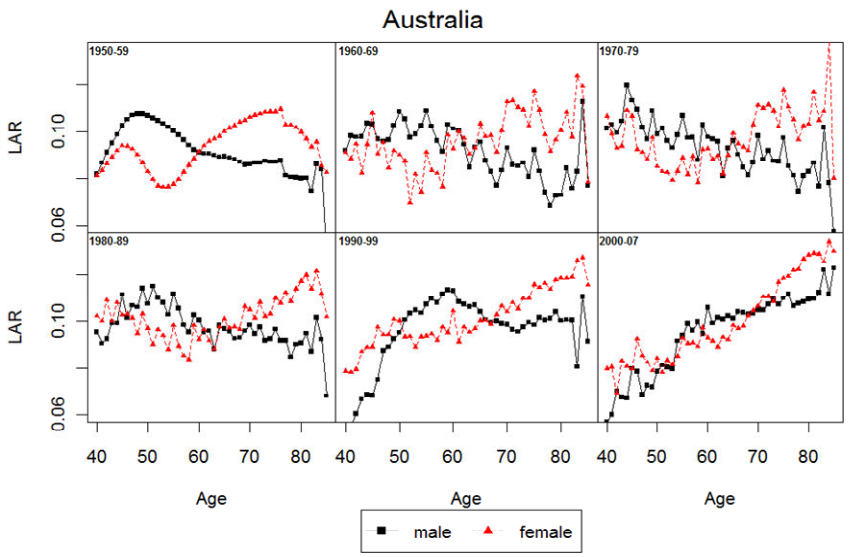
Table 1: BICs for the two-process model and the Gompertz model fitting to log mortality data between age 40 and 100

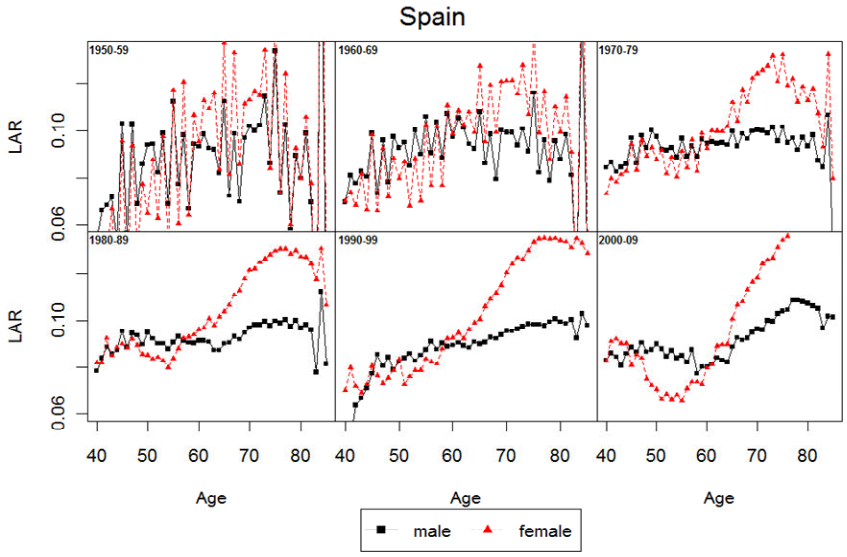
Population \ Model	**Two-process model**	**Gompertz model**
U.S. males period 1970	-313.80	-304.17
U.S. females period 1970	-334.88	-313.64
U.S. males period 2005	-360.62	-356.53
U.S. females period 2005	-318.75	-285.51
Swedish males cohort 1885	-283.65	-239.77
Swedish females cohort 1885	-265.27	-209.55
Swedish males cohort 1905	-238.25	-237.82
Swedish females cohort 1905	-224.46	-198.10

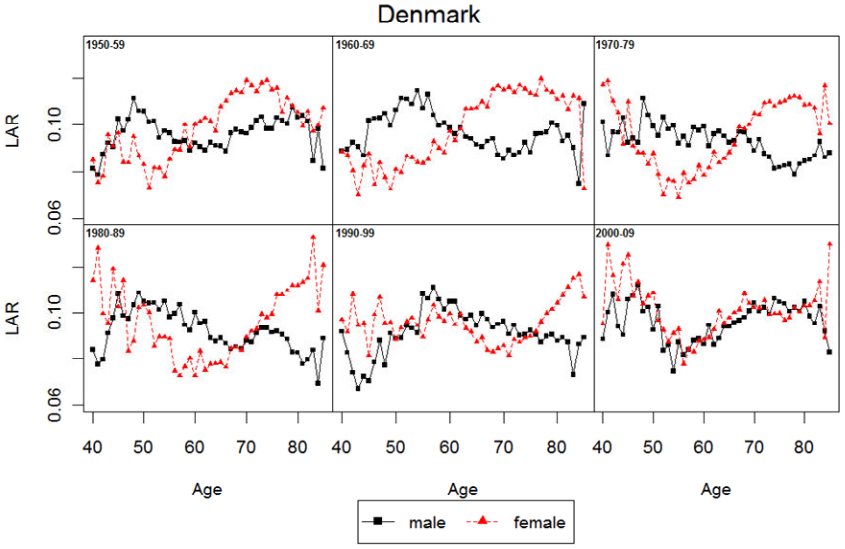
Figure 1: Period age-specific pattern of LAR from 16 selected industrialized countries in 6 periods (1950-1959,1960-1969,1970-1979,1980-1989, 1990-1999,2000-2007/8/9)



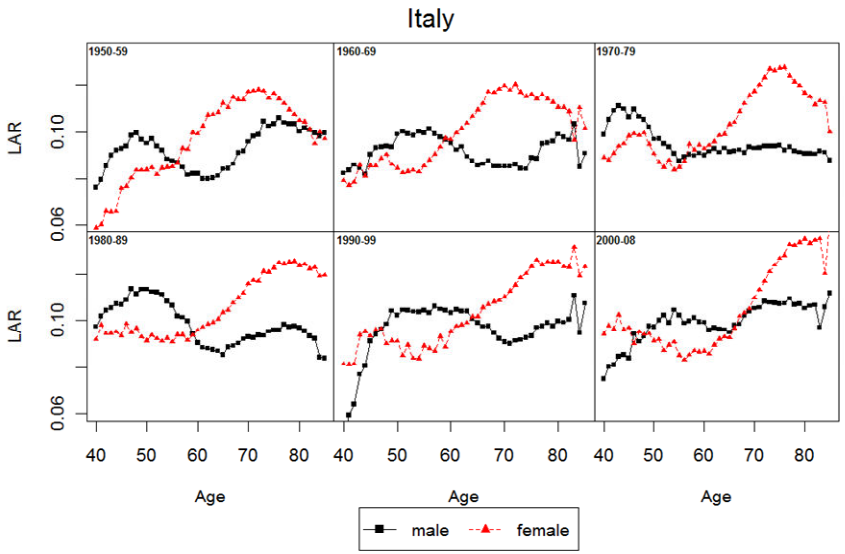

U.S.
1950-59
1960-69
1970-79
1980-89
1990-99
2000-07
LAR
0.06
0.10
40 50 60 70 80
Age
male
female

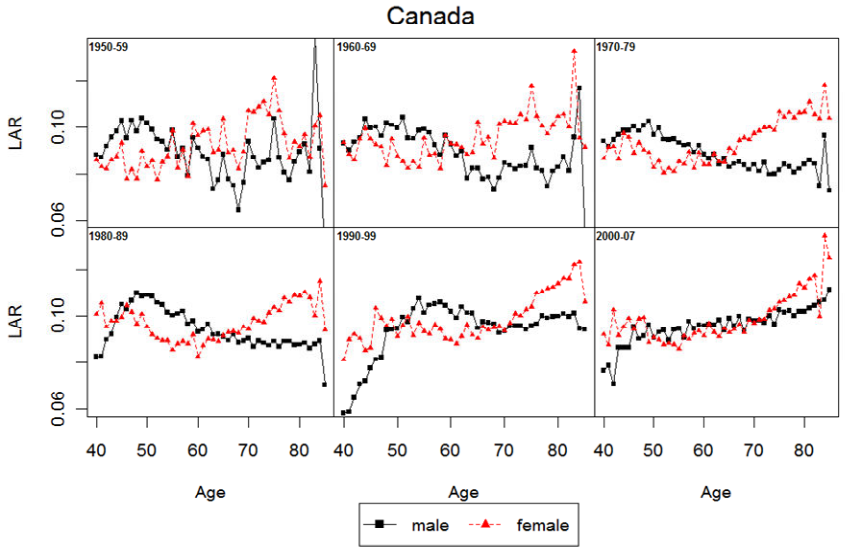

Australia
1950-59
1960-69
1970-79
1980-89
1990-99
2000-07
LAR
0.06
0.10
40 50 60 70 80
Age
male
female

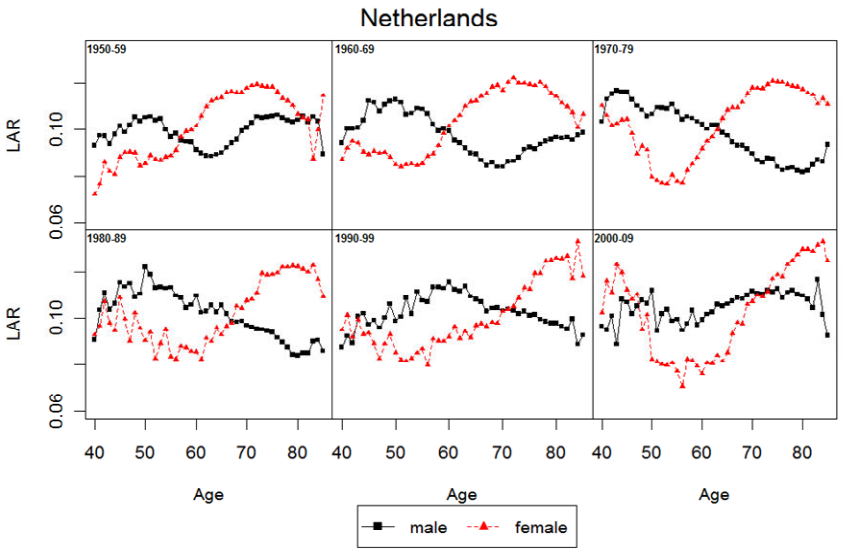

Spain
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
LAR
0.06
0.10
40 50 60 70 80
Age
male
female

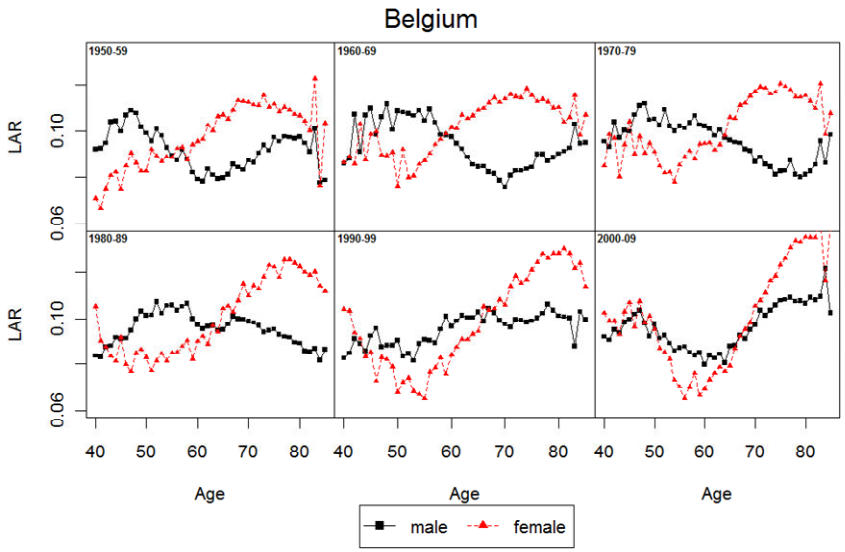

Denmark
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
LAR
0.06
0.10
40 50 60 70 80
Age
male
female

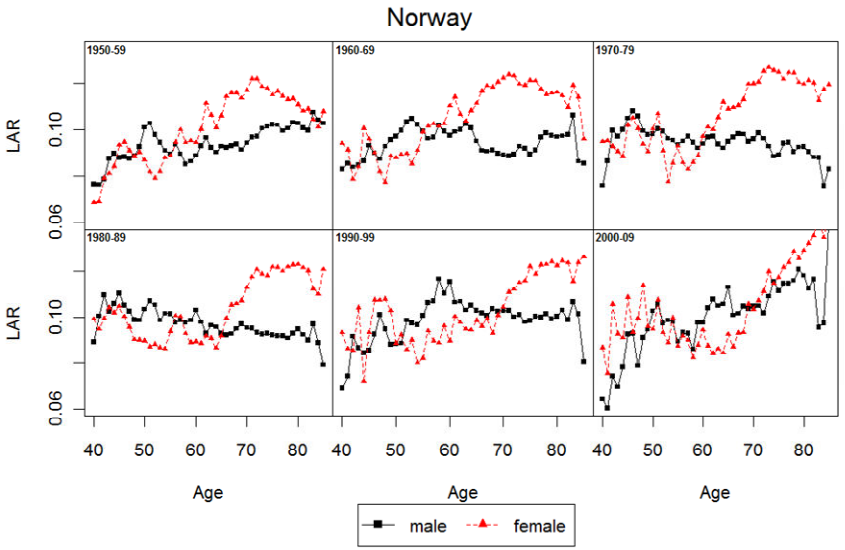

U.K.
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
LAR
0.06
0.10
40 50 60 70 80
Age
male
female

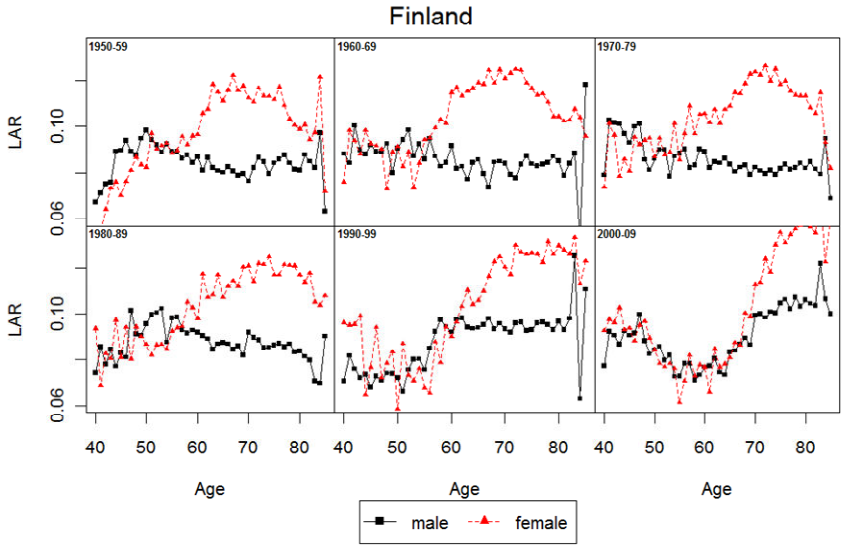

Italy
1950-59
1960-69
1970-79
1980-89
1990-99
2000-08
LAR
0.06
0.10
40 50 60 70 80
Age
male
female


Canada
1950-59
1960-69
1970-79
1980-89
1990-99
2000-07
LAR
0.06
0.10
40 50 60 70 80
Age
male
female


Netherlands
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
LAR
0.06
0.10
40 50 60 70 80
Age
male
female


Belgium
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
LAR
0.06
0.10
40
50
60
70
80
Age
male
female


Norway
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
LAR
0.06
0.10
40
50
60
70
80
Age
male
female


Finland
1950-59
1960-69
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1980-89
1990-99
2000-09
LAR
0.06
0.10
40
50
60
70
80
Age
male
female

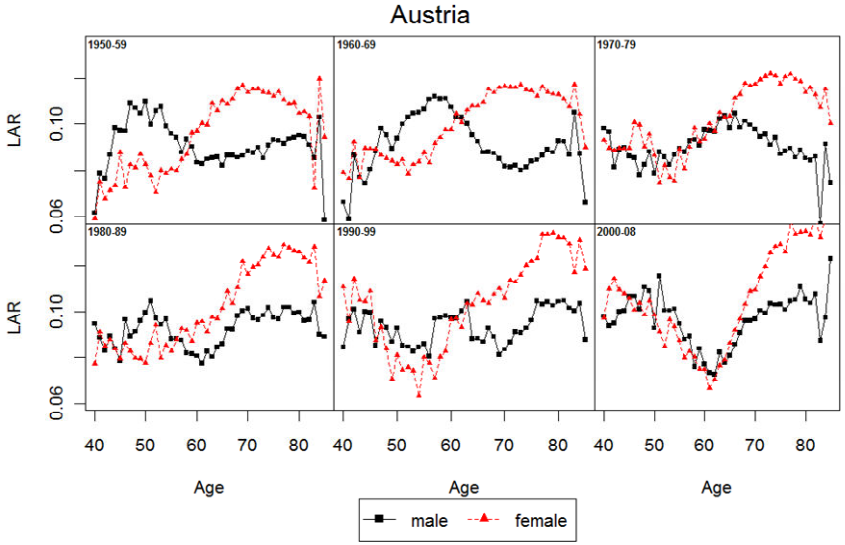
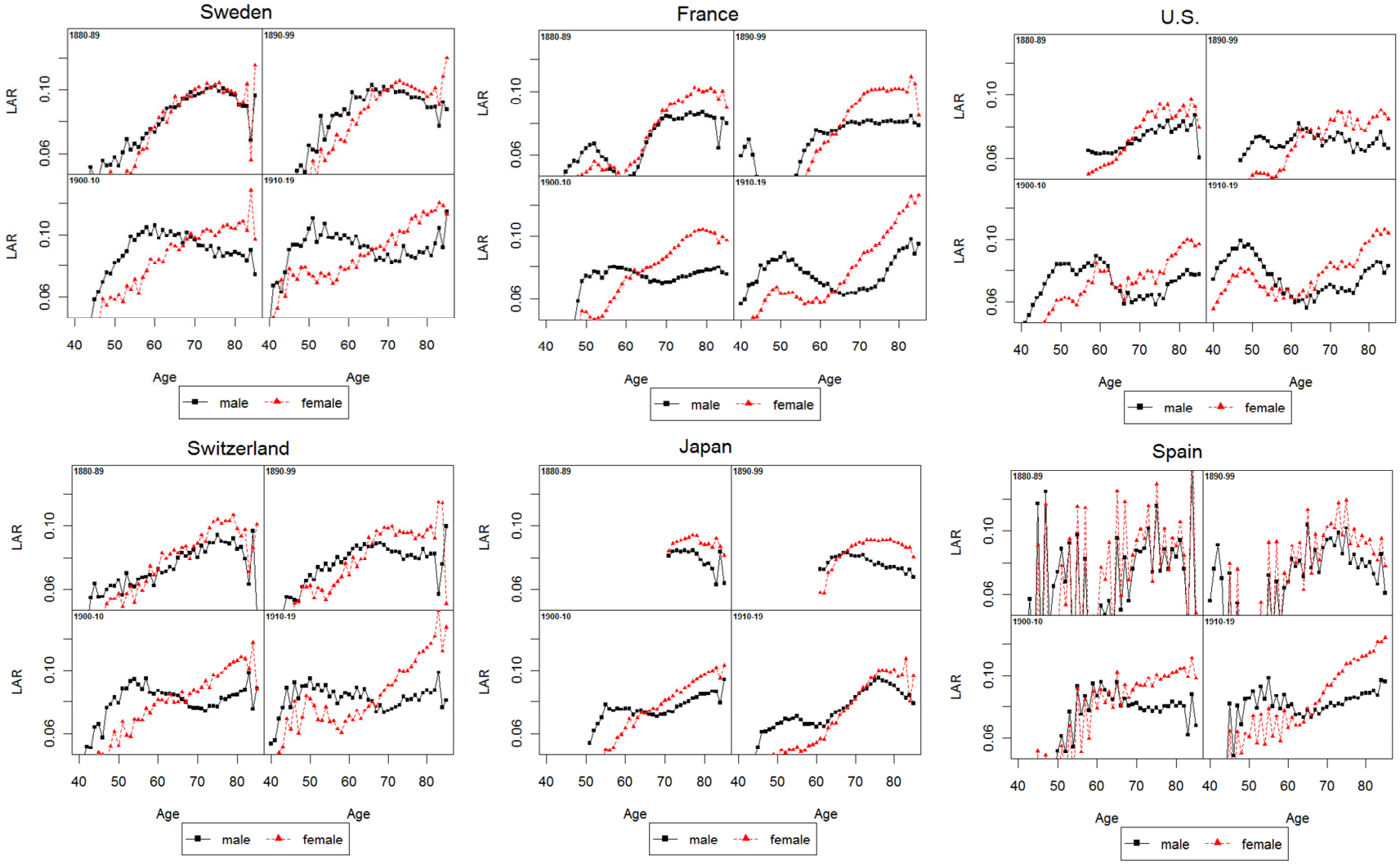
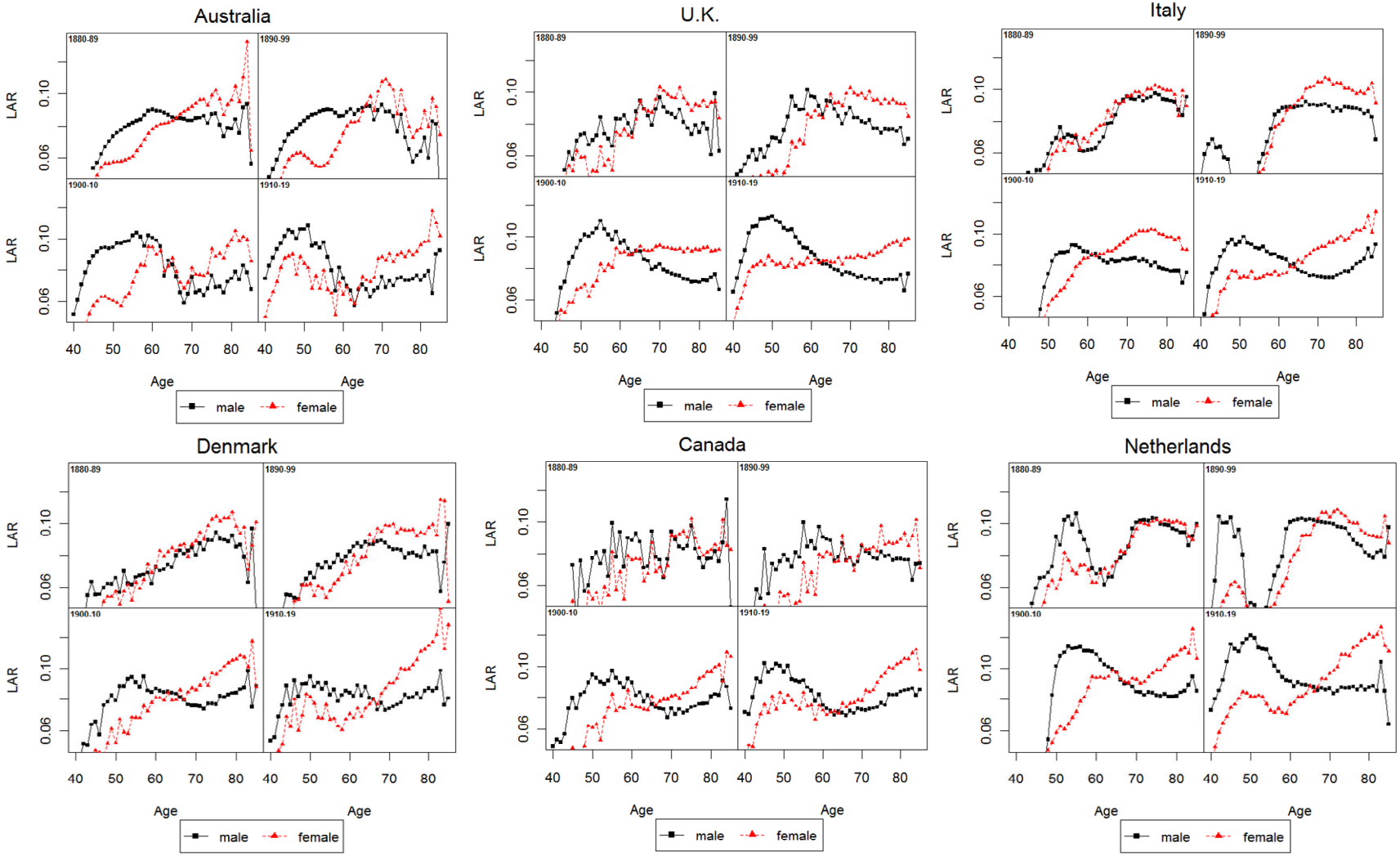
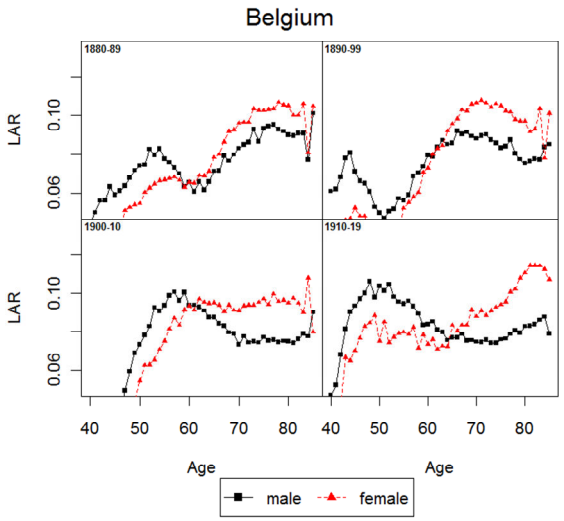

Austria
1950-59
1960-69
1970-79
1980-89
1990-99
2000-08
LAR
0.06
0.10
40
50
60
70
80
Age
male
female

Figure 2: Cohort age-specific pattern of LAR from 16 selected industrialized countries in 4 cohorts (1880-1889, 1890-1899, 1900-1910,1910-1919)




Australia
U.K.
Italy
Denmark
Canada
Netherlands
1880-89
1890-99
1900-10
1910-19
LAR
0.06
0.10
40
50
60
70
80
Age
male
female


Belgium
1880-89
1890-99
1900-10
1910-19
LAR
0.06
0.10
40
50
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70
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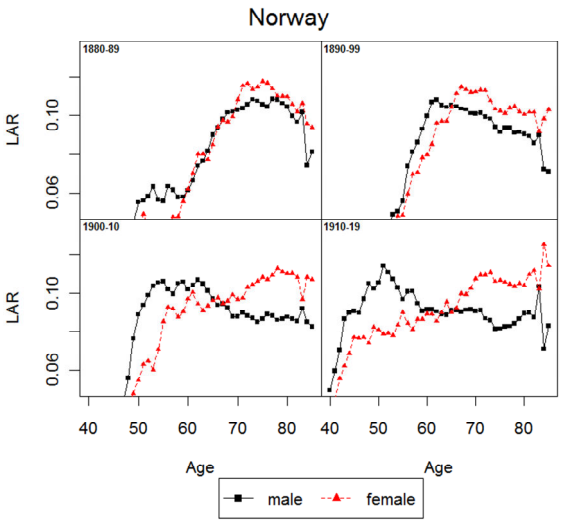
Age
male
female


Norway
1880-89
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LAR
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0.10
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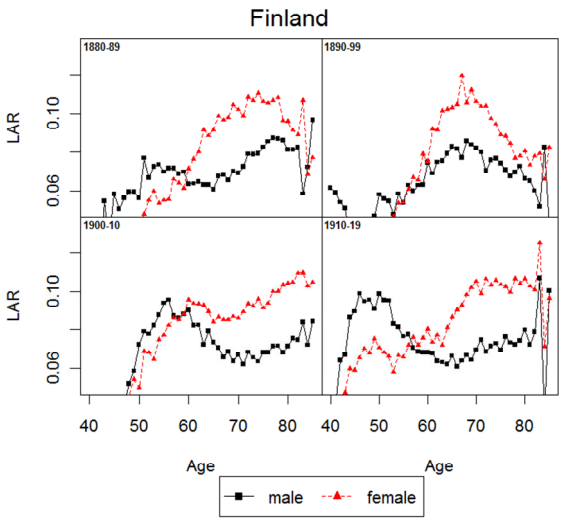
Age
male
female


Finland
1880-89
1890-99
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LAR
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Age
male
female


Austria
1880-89
1890-99
1900-10
1910-19
LAR
0.06
0.10
40
50
60
70
80
Age
male
female

Figure 3: Individual vitality declines stochastically and death occurs when vitality is exhausted through senescence ⓘ or when a random extrinsic challenge exceeds the remaining vitality ①.

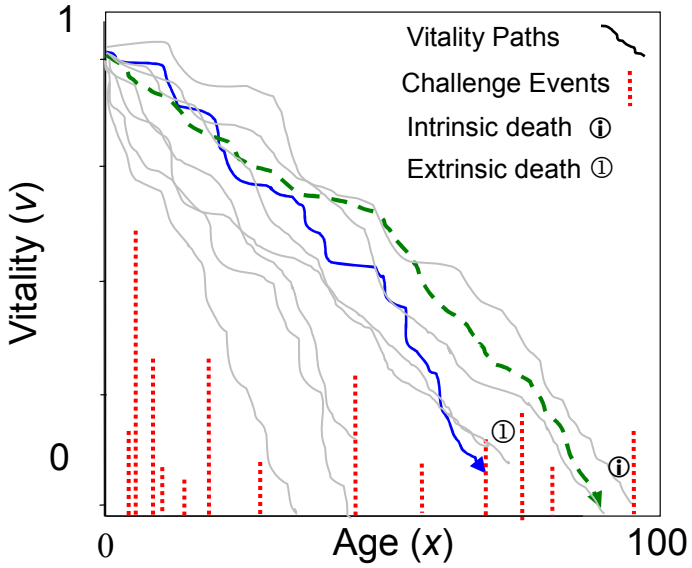


Figure 4: The two-process mortality model fits to the U.S. period data from year 1970 and 2005 for both males and females and the corresponding fitted LARs.

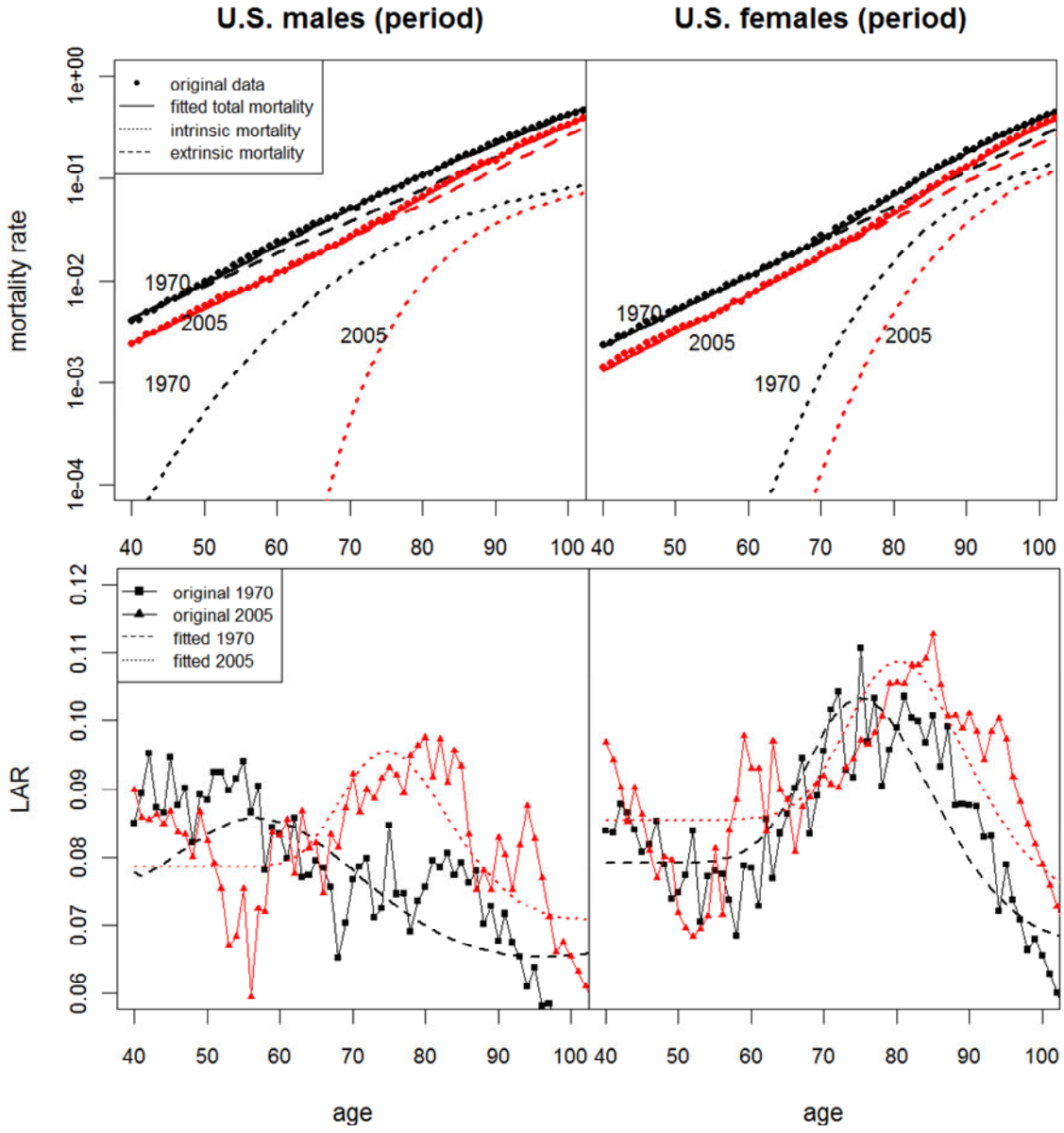
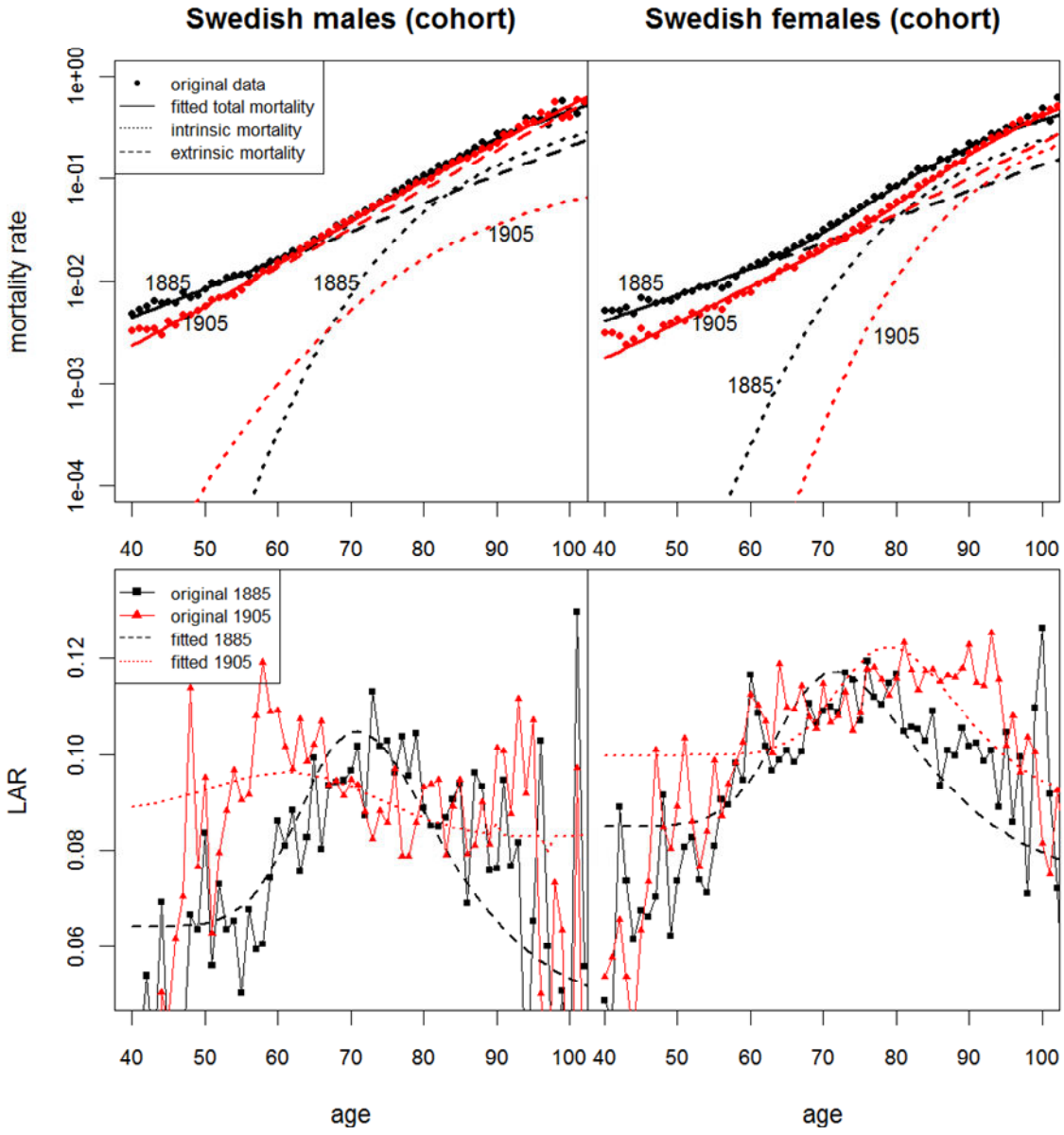


Figure 5: The two-mortality-process model fits to the Swedish cohort data from year 1885 and 1905 for both males and females and the corresponding fitted LARs



Supplementary Material: the two-mortality-process model

The two-mortality-process model represents total mortality as the sum of two death sources that result from different processes.

Intrinsic mortality

The intrinsic process summaries varied mechanisms by a single quantity called "vitality" to denote the remaining survival capacity of an organism. Each individual begins with an initial vitality, v_0, stochastically decline with age and intrinsic death occurs when its vitality reaches zero (figure 3). The random trajectory of vitality, v_x, between v_0 and 0 is described by the Wiener process:

$$dv / dx = -r + s\varepsilon_x \tag{S1}$$

where ε_x is a white noise process. When standardize eq. (S1) to the initial vitality v_0, the parameter r and s separately represent the fraction of vitality loss and the fraction of vitality spread per unit time. In this case, each normalized vitality trajectory starts from a single point v_0=1 and the actual differences in the initial values are reflected in the spread term s. To be specific, s demonstrates the average combined variation from both inherent (initial) and acquired (evolving) sources per unit time. The first-passage time of vitality to the zero boundary derived from eq. (S1) is the inverse Gaussian function (Cox and Miller 1965):

$$f(x) = \frac{x^{-3/2}}{s\sqrt{2\pi}} \exp\left(-\frac{(1-rx)^2}{2s^2 x} \right). \tag{S2}$$

By definition, the fraction of total population that has not died from intrinsic causes at age x, is equivalent to the probability that the individual's vitality has not reached zero by x. The survival pattern resulting from the intrinsic process can be expressed as

$$l(x) = 1 - \int_0^x f(x)dx = \Phi\left(\frac{1-rx}{s\sqrt{x}}\right) - \exp\left(\frac{2r}{s^2}\right)\Phi\left(-\frac{1+rx}{s\sqrt{x}}\right) \quad \text{(S3)}$$

and the intrinsic mortality rate is

$$\mu_i(x) = f(x)/l(x)\,. \quad \text{(S4)}$$

Extrinsic mortality

To model the extrinsic mortality, let Y_x with $x \geq 0$ be a random point process with rate λ to represent the occurrence of instantaneous extrinsic challenges such as a natural disaster or infection. In essence, λ measures the frequency of challenges. For each extrinsic event, a magnitude variable Z_x with a cumulative distribution function $\varphi(z)$ denotes the intensity of the challenge. We assume that only when the challenge magnitude Z_x exceeds the current vitality level v_x, the extrinsic challenge results in death, i.e. death occurs when $P_r(Z_x > v_x)$. Challenges not exceeding the current vitality level may also alter the vitality trajectory and in effect, nonlethal challenges are subsumed into r and contribute to the lifetime-averaged rate of change of vitality. This assumption couples the risk of death from external forces to the intrinsic age-dependent vitality level of the individual and insures that the effect of the extrinsic challenge changes with age. Assuming that Y_x is a history-independent Poisson process (Finkelstein 2007), the extrinsic mortality rate for each individual is

$$m_e(x) = \lambda \Pr(Z_x \geq v_x) = \lambda(1 - \varphi(v_x)) \quad \text{(S5)}$$

If we further assume that the magnitude of the event is exponentially distributed such that most external events are small and the probability of large events declines relative to their magnitude (Strehler and Mildvan 1960), then the cumulative distribution function is $\varphi(z) = 1 - e^{-z/\beta}$ where β is the scale parameter. Now the conditional extrinsic mortality rate for an individual given the realization of the vitality trajectory v_x becomes

$$m_e(x \mid v_x) = \lambda e^{-v_x/\beta} \tag{S6}$$

where β characterizes the environmental deleteriousness relative to the initial vitality of the organism. In essence, a larger β implies that high magnitude challenges occur more frequently.

The aggregated extrinsic mortality rates at a population level is

$$\mu_e(x) = \int_0^\infty m_e(x \mid v_x) g_x(v) dv_x = \int_0^\infty \lambda e^{-v_x/\beta} g_x(v) dv_x \tag{S7}$$

where $g_x(v)$ is the normalized conditional vitality distribution at time x when start with an initial value 1. Note that it is impossible to obtain an analytical solution for $g_x(v)$, because the extrinsic process unequally removes individuals from the population, it changes the original vitality distribution. We can only approximate it as

$$\mu_e(x) \approx \lambda e^{-(1-rx)/\beta} \tag{S8}$$

which simply expresses the average external killing rate as an exponential function of the mean vitality loss trajectory shaped by the two environmental parameters λ and β.

Combining eq. (S4) and eq. (S8), the total mortality rate equals:

$$\mu(x) = \mu_i(x) + \mu_e(x) \tag{S9}$$

Model fitting

The model fitting problem is cast as a maximum likelihood optimization, as developed by Salinger et al. (2003) to deal with interval-censored mortality data, in which mortalities are counted at the end of each time period rather than continuously. The likelihood function is constructed from the multinomial distribution based on the proportion of deaths in each time period.

$$\text{LogLik} = \sum_x \left(d_x \ln q_x + (n_x - d_x) \ln(1 - q_x) \right) \tag{S10}$$

where d_x is the number of deaths at age x, n_x is the number of population at the beginning of age x, and q_x is the probability of death at age x. The probability of death is derived from eq. (S9). The algorithm estimates standard errors thorough the estimated variance matrix. Specifically, standard errors are obtained by taking the square root of the diagonal elements in the inverse of the Hessian of the negative log-likelihood, evaluated at the parameter estimates (Kendall, Stuart and Ord 1977).