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RESEARCH ARTICLE

Compensation effect of mortality is a challenge to substantial lifespan extension of humans

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Abstract Despite frequent claims regarding radical extensions of human lifespan in the near future, many pragmatic scientists caution against excessive and baseless optimism on this front. In this study, we examine the compensation effect of mortality (CEM) as a potential challenge to substantial lifespan extension. The CEM is an empirical mortality regularity, often depicted as relative mortality convergence at advanced ages. Analysis of mortality data from 44 human populations, available in the Human Mortality Database, demonstrated that CEM can be represented as a continuous decline in relative mortality variation (assessed through the coefficient of variation and the standard deviation of the logarithm of mortality) with age, reaching a minimum corresponding to the species-specific lifespan. Through this method, the species-specific lifespan is determined to be 96–97 years, closely aligning with estimates derived from correlations between Gompertz parameters (95–98 years). Importantly, this representation of CEM can be achieved non-parametrically, eliminating the need for estimating Gompertz parameters. CEM is a challenge to lifespan extension, because it suggests that the true aging rate in humans (based on loss of vital elements, e.g., functional cells) remains stable at approximately 1% per year in the majority of human populations and is not affected by environmental or familial longevity factors. Given this rate of functional cell loss, one might anticipate that the total pool of functional cells could be entirely depleted by the age of 115–120 years creating physiological limit to human lifespan. Mortality pattern of supercentenarians (110 + years) aligns with this prediction.

Keywords Aging · Mortality · Gompertz law · Compensation effect of mortality · Coefficient of variation · Standard deviation

Introduction

The current gerontology literature is filled with ambitious claims about most humans potentially living to 120 or even 130 years. Some authors caution against "naive extrapolation, overhyped claims, and empty promises" (Le Bourg 2022a; Rattan 2024). Nonetheless, the question lingers: is radical life extension for humans genuinely achievable? Mathematical and statistical examinations of mortality patterns at extremely advanced ages suggest that there may not be a fixed limit to human lifespan (Gavrilov and

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Gavrilova 1991; Wilmoth 1997). However, the potential physiological constraints that could limit human survival should not be dismissed (Carnes et al. 2003). In this study, we explore a mortality pattern that could pose a challenge to extending human lifespan.

Background

An important manifestation of aging is an increased risk of death with advancing age and this mortality pattern is characterized by empirical regularities known as mortality laws (Gavrilov and Gavrilova 1991). One such regularity is the Gompertz–Makeham law describing human mortality or hazard rate (Golubev 2004; Olshansky and Carnes 1997):

$$\mu(x) = A + R \exp(\alpha x) \quad (1)$$

In Eq. (1) the first term (A) represents the age-independent or background mortality related to external mortality and acute infections. The second term is called the Gompertz function or senescent mortality. Here x is age, R and α are parameters called Gompertz intercept and Gompertz slope, since Gompertz function represents a straight line in semi-log coordinates.

Another mortality regularity is the Compensation Effect of Mortality (CEM), which refers to the relative mortality convergence at advanced ages (Gavrilov and Gavrilova 1991; Golubev 2019). According to CEM, higher values for the slope parameter α (in the Gompertz function) are offset (compensated) by lower values of the Gompertz intercept parameter R in different populations of the same species:

$$\ln(R) = \ln(M) - B\alpha \quad (2)$$

where B and M represent species-specific constants.

The term "compensation effect of mortality" was coined in 1978, coinciding with the accounting for the Makeham parameter, which led to significantly different parameter estimates for the Strehler–Mildvan correlation (Gavrilov et al. 1978). This effect is characterized by the relative convergence of senescent mortality patterns at advanced ages (Gavrilov and Gavrilova 1991; Gavrilov et al. 1978). CEM is not only evident in humans but also observed in some other species (Gavrilov and Gavrilova 1991; Golubev 2019; Shen et al. 2017).

Estimation of parameters B and M in Eq. (2) was conducted in 1991 and was based on 209 human populations. It found that the human species-specific lifespan is equal to 95 ± 2 years and species-specific mortality rate is equal to 0.51 year^{-1} (Gavrilov and Gavrilova 1991). Recent estimates of parameters B and M using data for contemporary populations showed that these estimates remain rather stable over time (Gavrilov and Gavrilova 2022).

CEM was initially demonstrated using the Gompertz parameters (Gavrilov and Gavrilova 1991). However, it's worth noting that the convergence of mortality trajectories in a semi-logarithmic scale (CEM) can be observed independently of the estimation of the Gompertz parameters for both period and cohort mortality data (Gavrilov and Gavrilova 2022, 2023). Figure 1 demonstrates CEM for six European populations of men and women using period mortality data for 2010. It can be noticed from Fig. 1 that at advanced ages variability of mortality (in a log scale) is lower compared to younger ages, so it was predicted that as mortality convergence is approached, a decrease in the relative variation of mortality is expected (Gavrilov and Gavrilova 2024).The purpose

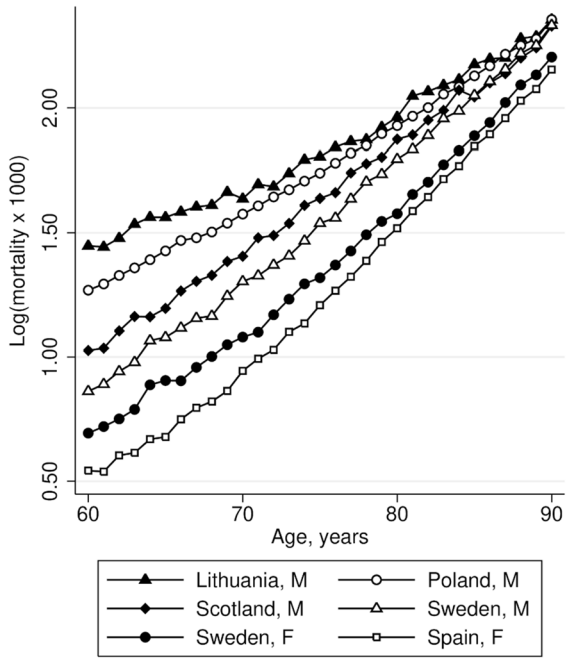

Fig. 1 Convergence of mortality trajectories at advanced ages for six European populations in 2010 illustrating compensation effect of mortality for males (M) and females (F)

of this study is to test this prediction and to discuss implication of CEM for human life extension.

Data and Methods

Data

Human Mortality Database (HMD) was used as a source of mortality data for this study (Human Mortality Database). This database contains mortality data for 44 countries and populations with reasonably good quality of demographic statistics. In this study we used period age-specific death rates in 2010 for 44 populations available in HMD. The age-specific period death rates of males and females are available in HMD from ages 0 to 110 in 1-year age and time increments. Deaths at age 110 and over are combined together.

Statistical Methods

The standard deviation of the logarithm of mortality and the coefficient of variation (which is the ratio of the standard deviation to the mean) for mortality were calculated as functions of age using age-specific death rates data from 44 populations as provided in the Human Mortality Database. All calculations were conducted using Stata statistical software, release 16.

Results and Discussion

We used two measures of variability: the standard deviation of the logarithm of mortality and coefficient of variation for mortality. In Fig. 2a, changes in the standard deviation of the logarithm of mortality across different ages are showed for men, women, and both sexes. It's notable that there's a significant reduction in variability at advanced ages, with trajectories reaching a minimum at age 97 years. Figure 2b illustrates similar trends for the coefficient of variation in mortality. The minimum coefficient of variation is observed at 97 years for men and women, and at 96 years for both sexes. Both curves exhibit a minimum around ages that align closely with known estimates of the human species-specific lifespan (Gavrilov and Gavrilova 1991, 2022).

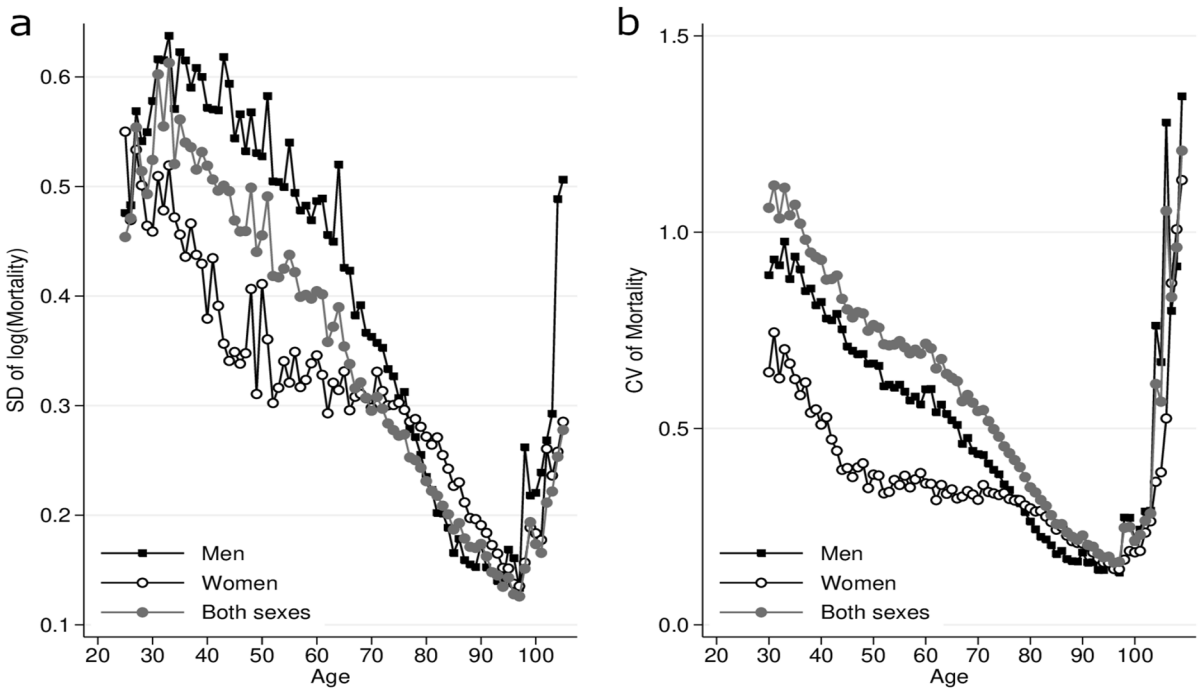

Fig. 2 Standard deviation of the logarithm of mortality in 44 human populations in 2010, by age (left panel). Coefficient of variation for mortality in 44 human populations, by age (right panel)

To further validate these findings, we conducted a comparison of mortality distributions (on a logarithmic scale) at young (30 years) and old (80 years) ages. Figure 3 shows that mortality variation is greater at younger ages compared to older ages for both men and women. At age 30 years, the standard deviation of the logarithm of mortality is 0.46 for women and 0.58 for men, while at age 80 years, these values decrease to 0.27 for women and 0.23 for men. Similarly, the coefficient of variation for mortality at age 30 years is 0.64 for women and 0.89 for men, and at age 80 years, these values decrease to 0.30 for women and 0.26 for men, respectively. Hence, the relative measures of dispersion for mortality are higher at younger ages.

In this study it was found that CEM can be presented in a non-parametric way (see Figs. 1, 2) as a reduction of relative variability of mortality with age. This approach allows us to obtain estimates of the species-specific lifespan without doing multiple calculations of the Gompertz–Makeham parameters. Non-parametric estimates of the species-specific lifespan are similar to ones based on the Gompertz parameters (Gavrilov and Gavrilova 1991, 2022; Milevsky 2020). These results show that calculating the Gompertz parameters is not needed to establish the existence of CEM and to estimate the species-specific lifespan.

There were assertions that the Strehler–Mildvan correlation arises as a result of statistical correlation between the Gompertz parameters suggesting that both this correlation and CEM are statistical artifacts (Tarkhov et al. 2017). The results of this study demonstrate that estimating the Gompertz parameters is unnecessary to establish the validity of CEM, thus rendering existing criticisms irrelevant. Another factor contributing to spurious correlations in Gompertz parameters occurs when dealing with small sample sizes. Simulation studies have revealed that conventional statistical approaches consistently underestimate the Gompertz slope and overestimate the Gompertz intercept parameters when sample sizes are small. However, the authors acknowledge that human demographers typically need not be concerned about these issues (Promislow et al. 1999). These challenges underscore the potential value of

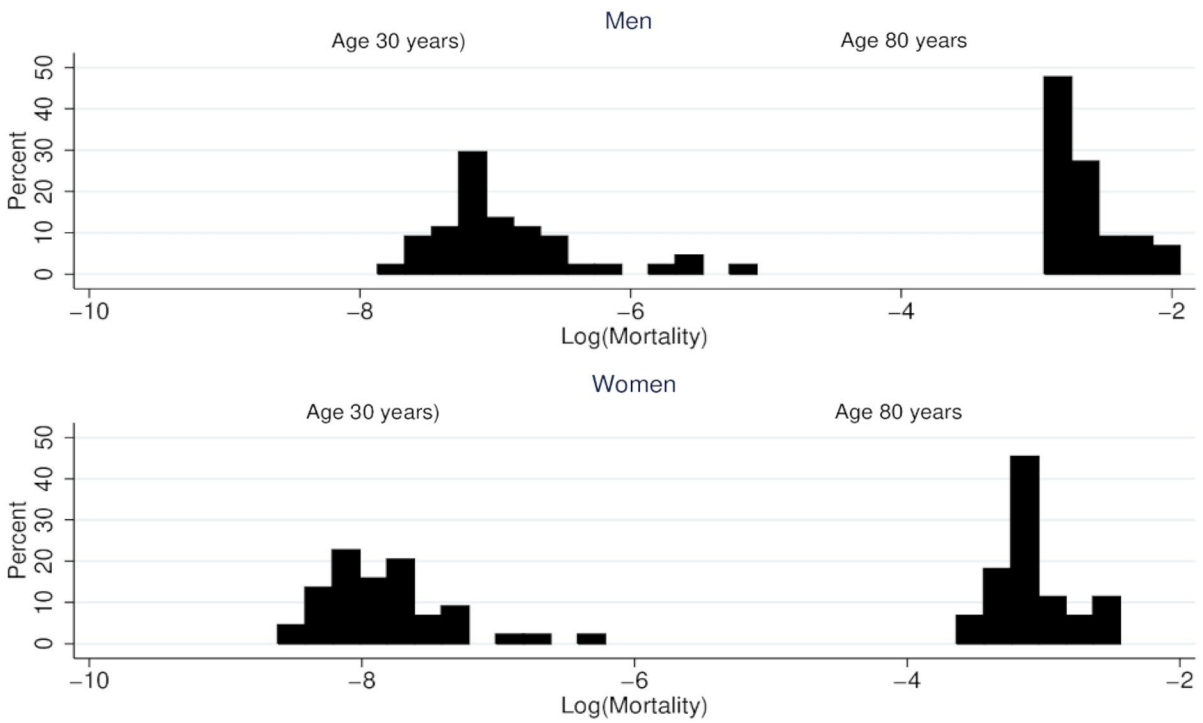

Fig. 3 Distribution of mortality (log scale) for younger (30 years) and older (80 years) individuals in 2010. Based on mortality data for 44 populations available in HMD

non-parametric methods for studying CEM that are not reliant on Gompertz parameter estimation.

CEM typically manifests when comparing various human populations distinguished by factors such as gender, income, familial longevity, race, and education (Gavrilova and Gavrilov 2022; Willcox et al. 2006). However, it's important to note deviations from this pattern. For instance, mortality among Japanese women deviates from CEM due to their combination of low initial mortality and a low actuarial aging rate. Consequently, the mortality rate of Japanese women at age 95 (the species-specific lifespan) is notably lower compared to other populations in the HMD, at 0.20 $year^{-1}$ versus a mean value of 0.29 $year^{-1}$ (95% Confidence Interval: 0.28, 0.31) for the rest of female populations. CEM is not observed when comparing the mortality of the same population at different points in time, as the Gompertz slope parameter (actuarial aging rate) remains stable over long historical periods (Gavrilov and Gavrilova 2022; Tai and Noymer 2018). Animal data present even more deviations from CEM. For example, Drosophila melanogaster exhibits two distinct groups of strains with differing parameters of CEM (Shen et al. 2017).

According to several reliability models of aging, CEM is only possible when the rate of redundancy loss of an organism with age (loss of vital elements, e.g., functional cells) is the same in all populations of a given species (Gavrilov and Gavrilova 1991, 2001). This treatment of CEM is not unique to these models, as it is consistent with other models as well (Avraam et al. 2013; Gavrilov 1978; Strehler and Mildvan 1960). In this scenario, human populations vary in the level of redundancy (reserves) of functional cells or other vital elements, with populations experiencing lower mortality having more reserves. Actuaries suggested using CEM to estimate the biological age of individuals within a specific population. Individuals from populations with a higher-than-average actuarial aging rate (Gompertz slope parameter) would have a lower biological age, while those from populations with a lower rate would have a higher biological age (Milevsky 2020).

Estimates of the species-specific lifespan may be of interest for aging studies, because they are related to the opportunity of estimating the rate of vital elements loss in human organism due to aging or true aging rate. According to reliability models of aging (Gavrilov and Gavrilova 1991, 2001), this rate is roughly equivalent to the inverse of the species-specific lifespan [1/B, B is derived from Eq. (2)]. It has been observed that the estimated species-specific lifespan for humans remains consistent over time, typically ranging between 95 and 98 years (Gavrilov and Gavrilova 1991, 2022; Milevsky 2020) or 96–97 years as determined in this study. Consequently, the estimated rate of vital element loss approximates 1% per year. Notably, this rate aligns with empirical estimates of annual cell loss in various neural tissues, ranging from 0.6 to 1.6% (Buetow 1971; Holland et al. 2012). The empirically estimated rate of telomere loss in peripheral blood mononuclear cells in humans is slightly lower at 0.5% base pairs per year (Whittemore et al. 2019), yet remains within a comparable magnitude. Additionally, research indicates that the rate of telomere loss is a species-specific characteristic, correlating with the lifespan of animal species (Whittemore et al. 2019).

Given this rate of functional cell loss, one might anticipate that the total pool of functional cells could be entirely depleted by the age of 115–120 years. Indeed, mortality among supercentenarians (those aged 110 + years), after a period of plateau, shows a sharp increase starting at age 113 years, making survival beyond the age of 117 years increasingly challenging (Gavrilova and Gavrilov 2020). Maximum reported age at death based on 2013–2070 mortality forecasts also stays at age around 115 years (Le Bourg 2022b). It looks like at these ages humans may face a barrier based on physiological limits (Carnes et al. 2003) even though statistically, there appears to be no definitive lifespan limit.

It appears that the convergence point of CEM remains stable despite a significant decline in mortality over the past 50 years, unaffected by factors reducing mortality at younger ages. Further studies have shown that CEM is evident across human populations with varying levels of familial longevity, including siblings of centenarians and siblings of those with shorter lifespans (Gavrilova and Gavrilov 2022). Consequently, familial longevity (and potentially the longevity genes associated with it) seems to have minimal or no impact on survival beyond the age of 100 years, which exceeds the species-specific lifespan. Due to CEM, factors linked to lifespan extension often lead to a paradoxical increase in the actuarial aging rate (the slope parameter of the Gompertz law), posing a challenge

to achieving significant lifespan extension. To identify populations with a slower aging process, one should seek those with both a slow actuarial aging rate and low initial mortality (the intercept parameter of the Gompertz law). These deviations from CEM might be of particular interest.

The representation of CEM obtained in this study serves as an additional empirical regularity that needs to be explained by mathematical models of aging. Such explanations can be offered by reliability theory of aging models (Gavrilov and Gavrilova 1991, 2001) or mathematical models combining heterogeneity and stochastic effects (Avraam et al. 2016, 2013).

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Author Contributions N.S.G. designed the study, conducted statistical analyses, and prepared the manuscript. L.A.G. analyzed and interpreted results, and edited the manuscript.

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Data Availability Mortality data are publicly available at the HMD website (www.mortality.org).

Declarations

Competing Interests The authors have not disclosed any competing interests.

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