One or more rates of ageing? The extended Gamma-Gompertz model (EGG)

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Abstract

Hidden heterogeneity poses serious challenges to survival analysis because the observed (aggregate) and the unobservable (individual) hazard functions may differ markedly from each other. However, the recent discovery of the so-called "mortality plateau" (i.e., the approximately constant value when mortality levels off, at very old ages) has brought new insights and pushed researchers towards the use of the gamma-Gompertz mortality model. Among the assumptions of this model, two are particularly relevant here: the shape, not the level, of the individual hazard function is a constant and so is the rate of ageing, i.e., the relative increase in mortality risks as people get older. The latter, however, does not pass empirical tests: the rate of ageing seems to vary (albeit only slightly) by age, gender, birth cohort and country.

In this paper, we propose a new model (EGG, or extended gamma-Gompertz) which overcomes this limitation by allowing the rate of ageing to increase gradually with age before converging to a constant value, as in Gompertz. While preserving all the fine theoretical and empirical properties of its simpler predecessor, the EGG model adapts better to empirical reality, i.e., in this paper, the mortality profile of the cohorts born between 1820 and 1899 in five countries with high-quality data. The advantages of this more refined mortality model are discussed.

1. Introduction

Since the first formulation of the proportional hazards model (Cox 1972), the concept of hazard function has acquired a pivotal role in survival analysis. This is due both to its interpretability (the instantaneous risk of experiencing death[1] on part of those who survived to time *t*) and its mathematical tractability, which, among other advantages, permits researchers to overcome the problems that derive from data incompleteness, such as censoring and truncation (Hanagal 2011).

Three broad ways of introducing covariates in hazard models can be distinguished (Finkelstein and Esaulova 2006). In *proportional* and *additive models*, the effect of a given covariate (e.g., being a smoker or doing regular gym) is to shift the entire hazard function up- or downwards. In the third type instead, *accelerated failure time models*, covariates are supposed to change the slope of the hazard function, i.e. how it varies with age (Kalbfleisch and Prentice 2002). Sometimes, a direct look at the data may suggest the best model, but this approach is justified only if all the individuals who share a given combination of observed covariates also share the same hazard function (homogeneity assumption; Wienke 2011).

Unfortunately, no empirical analysis can encompass all the relevant risk factors, some of which may be unknown. This leads to the problem of unobserved heterogeneity: those who share a given set of *observed* characteristics may differ in some other respect, and therefore in the susceptibility to experience the event of interest. To tackle the problem of unobserved heterogeneity, Vaupel et al. (1979) introduced *frailty* models.

In its simplest interpretation, frailty is an unobserved random factor that affects the individual risk of dying. It can be represented as the ratio between the hazard function of any individual "i" and that of a "standard of reference" (e.g., the average individual of that population). The notion of frailty may apply to any non-negative random variable: in practice, however, the most common distributions employed in empirical analysis are the gamma (Vaupel et. al. 1979), the inverse gaussian (Hougaard 1984) and the lognormal

[1] Or, in more general terms, "the event of interest". In survival analysis, however, this event is invariably death.

(McGilchrist and Aisbett 1991). A frailty model is thus a random-effects survival model, where frailty (the random effect) has a multiplicative effect on the base-line hazard function (Wienke 2011).

Despite the development of frailty models, the existence of unobserved heterogeneity poses some very serious challenges to the application of survival analysis, even in the simplest possible scenario of proportional hazards, where all the individuals share the same shape of the hazard function, but at different levels. Imagine that we can "follow" a cohort of apparently homogeneous individuals over time. Because of hidden heterogeneity, some of these individuals are in fact frailer than others, and destined to die earlier. The cohort will therefore undergo a compositional change, with the frailest less and less represented at older ages, and the shape of the aggregate hazard function, averaged over the survivors, will not be the same as that of the (assumedly unique) individual hazard function, which is not directly observable (Beard 1959; Vaupel et al. 1979). For the same reason, the simple observation of an aggregate hazard function will not give unique indications about the correct survival model to apply at the individual level (Vaupel and Yashin 1985).

The way out of this blind alley was found thanks to the combination of an empirical observation and a few theoretical developments. The empirical observation is the so called "mortality plateau", i.e., an (old) age starting from which aggregate mortality risks remain constant, instead of increasing (albeit at progressively slower rates) as they do before reaching the plateau. The existence of a plateau had been conjectured long before, by Greenwood and Irwin, in 1939. Only recently, however, have data become available to substantiate this conjecture (Thatcher, Kannisto and Vaupel 1998; Gampe 2010). Frailty theories may explain this apparently absurd phenomenon (Missov and Vaupel 2015): at very old ages, selection becomes so intense that it perfectly balances the increase in the force of mortality.

A few theorems proved that some important characteristics of the individual hazard functions and the distribution of frailty may be derived from how the aggregate hazard function behaves "asymptotically" (that is, at very old ages), because a mortality plateau is compatible with only a few survival models. For instance, Finkelstein and Esaulova (2006) proved that, if a plateau exists, human mortality cannot follow an accelerated failure time model. Missov and Finkelstein (2011) later proved that, if one uses an additive or a proportional hazard model, only a few frailty distributions are consistent with the formation of a mortality plateau. The gamma is, but the lognormal and the inverse-Gaussian, for instance, are not.

In the meantime, Missov and Finkelstein (2011) had proved that, if mortality approaches a plateau at older ages, frailty is characterized by a regular-varying density. Abbring and van den Berg (2007) proved that such distributions converge to gamma in proportional hazard models. In short, in proportional hazard models a wide range of initial frailty distributions eventually converge to gamma. Finally, Missov and Finkelstein (2011:68) found that if a plateau exists and mortality follows a proportional hazard model, the mortality hazard function is Gompertz-like. On these bases, Missov and Vaupel (2015:61) concluded that "the only meaningful solution at the plateau is provided by the gamma-Gompertz model", that is by a frailty model in which the individual hazard function follows the Gompertz (exponential) model and frailty is gamma-distributed.

The gamma-Gompertz is a proportional hazard model, which means that the shape (not the level) of the hazard function is the same for everybody, and so is the slope of the curve, known as the *rate of ageing*[2] and usually indicated by β (constant senescence hypothesis; Vaupel 2010).

[2] By "ageing", in this paper (as in the literature about these problems), we refer to the increase in mortality risks (or hazards) that is usually observed as people get older. In the exponential model that is usually adopted in this type of approach (see eqns. 12 and 13 below), the beta parameter associated with age provides an empirical measure of this increase and is also known as the rate of ageing. The rate of ageing is supposed to measure the rate of physiological deterioration due to the senescence process. Vaupel (2010) proposed the hypothesis that this parameter may be

Unfortunately, empirical tests about the constancy of the rate of ageing in real populations have thus far been rather disappointing. The parameter β seems to vary by gender and between cohorts born in different epochs and countries (Barbi 2003; Barbi et al. 2003; Salinari and De Santis 2014), or having gone through different historical experiences (Zarulli 2013). On top of that, its estimate is also affected by the age interval considered in the analysis (Carnes and Witten 2014; Salinari and De Santis 2015).

In this paper, we submit that the variability in the estimates of the rate of ageing stems from an oversimplification of reality, coupled with an incorrect choice of the starting age of the analysis. The individual rate of ageing is assumed to be constant not only across different individuals but also across ages, which is not a necessary characteristic of the model: it is merely a mathematical (over)simplification, which, incidentally, runs counter to what the empirical (aggregate) evidence suggests. Ageing is virtually zero (i.e., mortality is roughly constant) between approximately 25 and 45 years (Gurven and Kaplan 2007; Carnes and Witten 2014; Salinari and De Santis 2015; Engelman et al. 2017). After that, the individual rate of ageing increases but not necessarily at a constant rate (mortality acceleration; Horiuchi and Wilmoth 1998). Later still, ageing *must* stabilize at some constant level, otherwise the mortality plateau (starting somewhere between 110 and 120 years) would not be observed (Missov and Vaupel 2015).

The discussion of the mechanisms that cause the rate of ageing first to increase with age and then to stop at a given (maximum) value goes beyond the scope of this paper: let us just say that it may depend on the complex system of maintenance and repair that counters deterioration at the cell level, with less and less success as time goes by (Horiuchi 2003). Whatever the underlying reason (biological or of a different nature), the outcome is, we submit, that the rate of ageing increases gradually with age following an S-shaped function (think of a logistic curve, as a first approximation). If this is true, the use of a constant value for ageing (the slope of the increase in individual mortality risks) instead of a function that becomes constant only at the end of a process (logistic), results in estimates that depend on the age interval that one considers.

Conversely, a more flexible model, as the Extended Gamma-Gompertz model (EGG) that we are proposing here, can describe the evolution of mortality in virtually any age interval after the onset of mortality acceleration. Note that the EGG model converges to a gamma-Gompertz model at older ages, thus preserving all its fine asymptotic properties, the most important of which is that it eventually generates a mortality plateau.

We applied our model to the evolution of mortality of the cohorts born between 1820 and 1899 in five Northern European countries with good data taken from the Human Mortality Database,[3] where "good" means both long (up to 109 years of age) and of high quality. Our model captures the main historical trends of mortality, and produces an age schedule of the rate of ageing that is virtually independent of the country and year of birth. However, some (minor) differences between men and women remain.

The paper is organized as follows: the second section presents the gamma-Gompertz (GG) model. The third section presents the extended gamma-Gompertz (EGG) model. The fourth section focuses on the identification of the best functional form for the description of the evolution of the rate of ageing with age (our extension E of the original GG model). The fifth section presents the analysis of the evolution of ageing in five countries (the Nordic ones plus the Netherlands) between 1820 and 1899. In the final section, we briefly discuss the results of our analysis.

constant across individuals and over time. In this paper we will refer to such hypothesis as the constant senescence hypothesis.

[3] We did not include the cohorts born after 1900 because we wanted to study mortality up to very old ages (109 years, in this case).

2. The gamma-Gompertz model

In survival analysis, the survival function *s(x)* is a non-increasing right-continuous function, indicating the probability that death occurs at an age greater than *x*. The hazard function *μ(x)* expresses the age-specific risk of dying during the next instant of time for those who survived to age x

$$\mu(x) = -\frac{s'(x)}{s(x)} = -\frac{\partial \ln[s(x)]}{\partial x}. \quad (1)$$

The cumulative hazard function M(x) is

$$M(x) = \int_0^\infty \mu(x)dx = -\ln[\mathrm{s(x)}], \quad (2)$$

which leads to

$$s(x) = e^{-M(x)}. \quad (3)$$

Under the assumption of *homogeneity*, the individual and the aggregate (cohort) hazard functions are the same. This allows researchers first to estimate the aggregate hazard function (for instance, with a Kaplan-Meier estimator) and then to use it at the individual level (for instance, with a proportional hazard model). Things change, however, if the assumption of homogeneity does not hold.

Assuming that an individual has a specific level of frailty *z* and that frailty affects the baseline hazard function *μ(x)* in a multiplicative way (proportional hazards), the individual hazard function *μ(x, z)* can be written as follows:

$$\mu(x, z) = z\mu(x). \quad (4)$$

In eq. (4), frailty is the (positive) ratio between the hazard function of an individual and the baseline hazard function for the standard individual of the cohort. Frailty models usually assume that neither individual hazard functions nor frailty are observable. What can be observed is the average hazard function $\bar{\mu}(x)$

$$\bar{\mu}(x) = \int_0^\infty z\mu(x)f(x, z)dz = \mu(x)\bar{z}(x), \quad (5)$$

where $f(x, z)$ is the probability density function of z among the survivors to age x. Similarly to eq. (3), the average survival function emerges as

$$\bar{s}(x) = \int_0^\infty e^{-M(x)z} f(x = 0, z)dz. \quad (6)$$

As frailer individuals tend to die earlier, the average frailty $\bar{z}(x)$ decreases with x. The aggregate hazard function $\bar{\mu}(x)$ of eq. (5) will thus increase at a slower pace than its correspondent at the individual level.

Well before the emergence of frailty models, several scholars had noticed that, at older ages, (aggregate) human mortality deviates from the expected exponential trend (see Olshansky 1998 for a list). However, only in the '90s were data systematically collected on mortality also at advanced ages (Thatcher, Kannisto and Vaupel 1998). The database thus created showed a marked deceleration of ageing after the age of 80 years (Vaupel 1997; Vaupel et al. 1998). Incidentally, ageing decelerates among the very old also in other living species, such as medflies (Carey et al. 1992), Caenorhabditis elegans (Vaupel et al. 1994), Mediterranean fruit flies (Carey, Liedo and Vaupel 1995) and yeasts (Jazwinski et al. 1998; Vaupel et al. 1998), and this deceleration is generally considered the strongest indication of the existence of hidden heterogeneity.

The gamma family of frailty models assumes that frailty is distributed as a standardized gamma $Z \sim \Gamma(\lambda, \kappa)$, with parameters $\lambda = \kappa = \frac{1}{\sigma^2}$, where σ^2 is the initial variability of frailty. This condition is necessary to make the model identifiable, because it leads to $E(Z) = \frac{\lambda}{\kappa} = 1$ and $var(Z) = \frac{\lambda}{\kappa^2} = \sigma^2$.

The choice of the gamma distribution to model frailty can be justified on the basis of four main considerations:

1) gamma is a flexible distribution which may assume different shapes, from exponential to bell-shaped;
2) in a wide family of univariate frailty models the distribution of frailty converges to a gamma under mild assumptions (Abbring and van den Berg 2007; Wienke 2011);
3) the gamma distribution is compatible with the mortality plateau (Missov and Vaupel 2015);
4) if frailty is gamma-distributed at age x, it is gamma-distributed also among the survivors to age x+1, and among those who die between x and x+1 (Vaupel et al. 1979).

The average survival function (eq. 6) represents the Laplace transform of the probability density function of z evaluated at the cumulative baseline hazard (Vaupel and Missov 2014). Knowing that the Laplace transform of the gamma distribution is

$$\left(\frac{k}{k+s}\right)^{\lambda}, \tag{7}$$

where s indicates the Laplace variable, and assuming a gamma-distributed frailty, we get

$$\bar{s}(x) = \int_0^{\infty} e^{-M(x)z} f_x(z)dz = \mathcal{L}_Z[M(x)] = \left[\frac{\kappa}{\kappa+M(x)}\right]^{\lambda}. \tag{8}$$

Remembering that $\lambda = \kappa = \frac{1}{\sigma^2}$, we can rewrite (8) as:

$$\bar{s}(x) = [1 + \sigma^2 M(x)]^{-\frac{1}{\sigma^2}}. \tag{9}$$

Using the definition of the hazard function of eq. (1), the assumption that frailty is gamma-distributed leads to the following average hazard:

$$\bar{\mu}(x) = -\frac{\partial \ln[\bar{s}(x)]}{\partial x} = \frac{\mu(x)}{1+\sigma^2 M(x)}. \tag{10}$$

Observing, from eq. (9), that $[1 + \sigma^2 M(x)]^{-1} = [\bar{s}(x)]^{\sigma^2}$, eq. (10) can be rewritten as follows

$$\bar{\mu}(x) = \mu(x)[\bar{s}(x)]^{\sigma^2}. \tag{11}$$

The gamma-Gompertz model starts from the assumption of a gamma-distributed frailty and adds the condition that the baseline hazard follows the Gompertz model:

$$\mu(x) = \alpha e^{\beta x}, \tag{12}$$

where α represents the initial level of mortality and β - the rate of ageing - indicates how fast mortality increases with age. Substituting eq. (12) into eq. (11) and taking the logarithm, we get

$$\ln[\bar{\mu}(x)] = \ln \alpha + \beta x + \sigma^2 \ln[\bar{s}(x)], \tag{13}$$

which is the conventional representation of the gamma-Gompertz model.

The estimation procedure for the gamma-Gompertz model assumes that the death counts at age x are Poisson-distributed (Brillinger 1986)

$$D_x \sim Poisson(E_x \bar{\mu}_x), \tag{14}$$

where D_x and E_x indicate respectively the number of deaths and the exposures at age *x*. Under this assumption, the three parameters of the gamma-Gompertz models can be estimated by maximizing the Poisson log-likelihood:

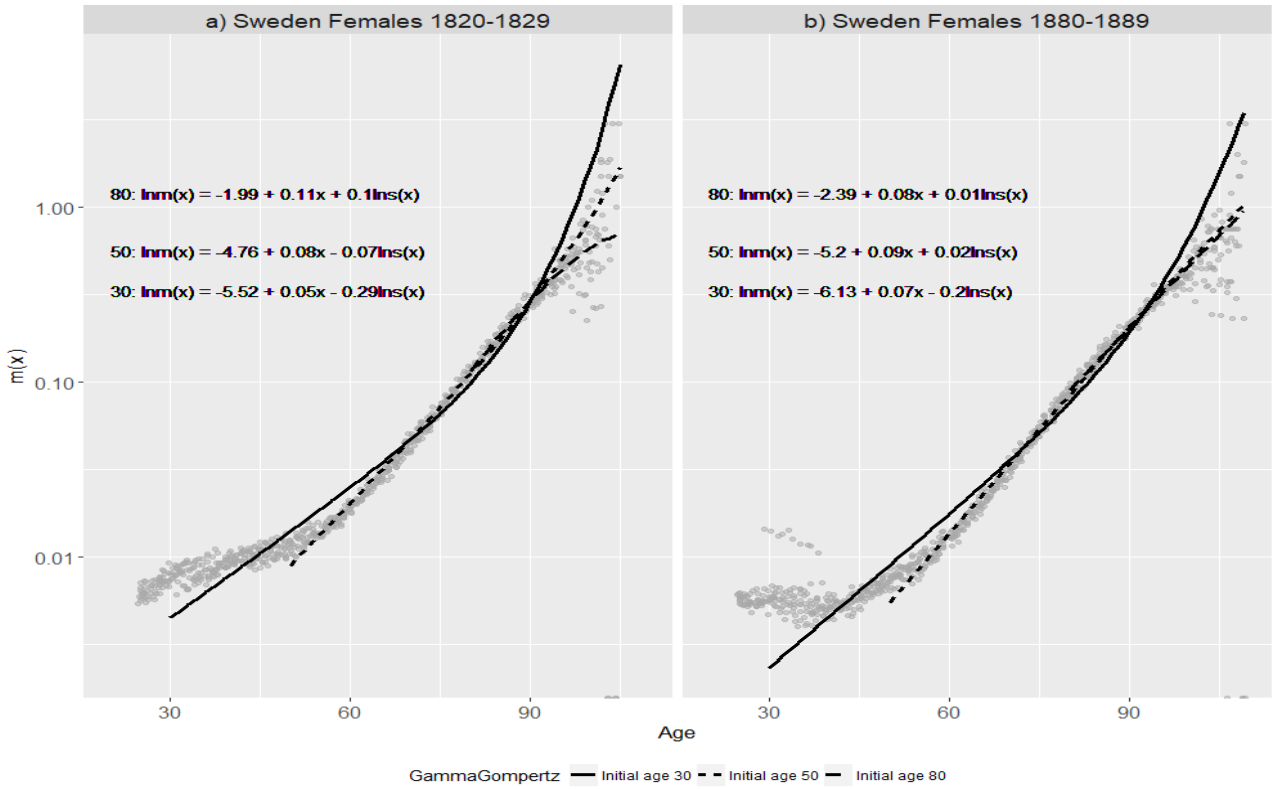
$$\ln[L(\alpha,\beta,\sigma^2)] = \sum_x [D(x)\ln(\bar{\mu}(x)) - E(x)\bar{\mu}(x)]. \quad (15)$$

Summing things up, the gamma-Gompertz model relies on four hypotheses:

a) frailty does not change over time
b) frailty affects the baseline hazard multiplicatively
c) frailty is gamma-distributed
d) the baseline hazard follows the Gompertz model.

The first assumption was empirically tested and confirmed on Danish twins, at least from age 30 onwards (Yashin and Iachine 1997; Vaupel et al. 1998). The last three assumptions have found indirect support in the recent discovery of the human mortality plateau (Missov and Vaupel 2015). However, some of the assumptions underpinning the gamma-Gompertz remain questionable. Assumption (d), for instance, implies that the rate of ageing is constant in human populations (Vaupel 2010), which is not confirmed in empirical analyses. Furthermore, the use of the Gompertz model as the baseline hazard function contradicts the observation that (aggregate) mortality is almost constant between about 25 and 45 years, and starts to increase only at older ages (see, e.g., Figure 1b). When the gamma-Gompertz model is estimated from 80 years onwards it produces an excellent description of the evolution of mortality. Instead, with a starting age of 30 or 50 years, the fit deteriorates considerably, and results in an estimate of the initial variance that is negative and significant. This illogical outcome stems from the fact that, around 75 years, the data present an inflection point which marks the transition from a phase of mortality acceleration to a phase of mortality deceleration. The gamma-Gompertz model, however, has no inflection point, which implies that it can be used to model human mortality only beyond the inflection point, after the onset of the deceleration phase.

Figure 1. *Fitting of the gamma-Gompertz model with different choices of the initial age (30, 50 or 80 years; Sweden, females, selected birth cohorts)*



Note: When the analysis starts at age 30, the mean squared errors (MSE) are: $MSE_{(30)1820}$=0.328, $MSE_{(30)1880}$=0.195. When the analysis starts at later ages, we get $MSE_{(50)1820}$=0.046, $MSE_{(50)1880}$=0.033, $MSE_{(80)1820}$=0.117, and $MSE_{(80)1880}$=0.065.

3. Extending the Gamma-Gompertz model

In order to overcome the limitations of the gamma-Gompertz model, we modelled the baseline hazard function from, let us say, 30 years onwards as follows

$$\mu_{egg}(x) = \alpha e^{F(x)\beta x}, \qquad (16)$$

where the new term F(x) – a sort of ageing "dimmer" - represents a cumulative distribution function (CDF) whose functional form is still to be identified (readers may think of a logistic, as a first approximation). At young ages, F(x) is (very close to) zero, so that model (16) reduces to $\mu(x) = \alpha$, with constant mortality. At some point, F(x) starts to increase with age, which affects the rate of ageing (the exponent of eq. 16). At older ages, F(x) tends to 1, and model (16) converges to Gompertz, as in eq. (12). The aim of the ageing dimmer F(x) is thus to model the emergence of ageing, which is a complex biological process that requires time to develop fully. Model (16) can be regarded as a state-dependent model where the effect of age on the force of mortality $F(x)\beta$ becomes more and more noticeable as one gets older.

With the introduction of the "dimmer" F(x), the interpretation of the parameters α and β changes slightly with respect to the original Gompertz model: α represents the force of mortality of a young individual, when demographic ageing is (practically) absent. Therefore, we will refer to this parameter as "initial mortality". The β parameter, instead, represents the limit value of the rate of ageing (at very old ages), while, between these two extremes, the age-dependent rate of ageing is $F(x)\beta$ ($0 \le F(x) \le 1$). Vaupel's (2010) hypothesis can therefore be reformulated as follows: the age-schedule of the rate of ageing $F(x)\beta$ is a constant (e.g., by country, or birth cohort, or gender), even if ageing changes with age, because of the term $F(x)$.

One of the problems with eq. (16) is how to determine the functional form of the ageing dimmer. We compared seven different cumulative distribution functions (CDF's): Beta, Gamma, Exponential, Inverse Gaussian, Lognormal, Normal and Weibull. As both the Exponential and the Beta resulted in a comparatively poor fit (not shown here), we dropped them from the analysis and focused on the remaining five distributions.

In order to estimate model (16) with collective (cohort) data on mortality, we assumed that frailty is gamma-distributed among the individuals of a cohort and we inserted eq. (16) into eq. (10)

$$\bar{\mu}_{egg}(x) = \frac{\mu_{egg}(x)}{1+\sigma^2 M_{egg}(x)}. \qquad (17)$$

To determine the value of the cumulative hazard function $M_{egg}(x)$ necessary to estimate eq. (17) we resorted to numeric integration of eq. (16).

Wrapping things up, in order to determine $\bar{\mu}_{egg}(x)$ we need to estimate five parameters: the initial force of mortality (α), the asymptotic rate of ageing (β), the initial variance of frailty (σ^2), and the two parameters θ_1 and θ_2 that define the specific functional form of the ageing dimmer (all the CDF's considered here are characterized by two parameters).

The five parameters of eq. (17) can be estimated from the average force of mortality by assuming that deaths are Poisson-distributed (Brillinger 1986). The corresponding log-likelihood is

$$\ln L(\alpha, \beta, \sigma^2, \theta_1, \theta_2) = \sum_x \big(D(x)\ln\bar{\mu}_{egg}(x) - E(x)\bar{\mu}_{egg}(x)\big), \qquad (18)$$

which can be maximized numerically. The best functional form for the ageing dimmer is the one that yields the largest log-likelihood.[4]

The estimation of the model parameters allowed us to identify three basic characteristics of adult mortality: two threshold ages for the ageing transition (its onset and its turning point, i.e. mortality deceleration) and the asymptotic probability of death (i.e., constant level of risk, at very high ages, at the aggregate level).

Mortality acceleration onset. To compute the age when the process of mortality acceleration becomes detectable we need to choose an arbitrary, but very small threshold T_α (e.g., 0.05). The age x_α when demographic ageing begins can then be defined as the age when the rate of ageing equals 100*T_α percent of its maximum ($x_\alpha: F_{x_\alpha} = T_\alpha$). We also have to take into account the "young mortality hump", a mortality increase that occurs at young adult ages. A recent paper by Engelman, Seplaki and Varadhan (2017) devoted to the analysis of the so-called "quiescent phase of human mortality" (broadly speaking, the age interval between adolescence and middle age) led these authors to identify the end of the mortality hump and the beginning of mortality acceleration at about 30-35 years. In the case of women, maternal mortality, which extends well into the forties, can also bias our estimates.[5] To avoid this potential source of bias, we decided to run our analysis with two different starting ages: 30 (our preferred choice) and 50 years. Incidentally, the comparison of the results of these two cases gives an idea of the implications of choosing different starting ages for the analysis.

Mortality deceleration onset. The age when mortality deceleration begins x_d is, mathematically, an inflection point of the hazard function, where the second order derivative is zero. Therefore, we considered the log-transformed hazard function and differentiated it twice with respect to age:

$$\delta(x) = [\ln\bar{\mu}_{egg}(x+1) - \ln\bar{\mu}_{egg}(x)] - [\ln\bar{\mu}_{egg}(x) - \ln\bar{\mu}_{egg}(x-1)]. \qquad (19)$$

As the $\ln\bar{\mu}_{egg}(x)$ series first accelerate and then decelerate, the $\delta(x)$ series should be positive up to the inflection point and negative at older ages. Therefore, we looked for the highest age at which the $\delta(x)$ series were positive. Following Horiuchi and Wilmoth (1998), we expected the mortality deceleration process to begin between 70 and 80 years.

Asymptotic mortality. As for the probability of death at the plateau, we simply used eq. (17) to estimate the force of mortality at the beginning of ageing stationarity.[6] We expected this value to be constant among the cohorts born in the 19th century, and the value itself to be close to 0.5, as indicated by Gampe (2010).

This procedure can also be used in the process of model selection. If the parameters estimated by the use of a given CDF in the EGG model are far from the empirically observed values (for instance the value of 0.5 for asymptotic mortality), that CDF can reasonably be discarded.

Finally, to verify the constancy of the age-specific rates of ageing we regressed our estimates of the age-specific rate of ageing on several cohorts' characteristics:

$$\boldsymbol{b} = \boldsymbol{X}\boldsymbol{\varphi} + \boldsymbol{\epsilon}, \qquad (20)$$

where **b** is the vector of estimated age-specific rates of ageing, **X** is the regressors matrix, $\boldsymbol{\varphi}$ is the parameters vector and $\boldsymbol{\epsilon}$ is the error term. As regressors (**X**) we used the year of birth, the country, gender and the interaction between gender and age. We introduced also the interaction term to take into account the possibility that the evolution of the rate of ageing with age differs between males and females. If the rate of

[4] We verified that the ranking does not change with alternative criteria and measures, such as maximum likelihood, AIC or BIC (not shown here).

[5] This possibility was suggested by one of the reviewers which we thank for that.

[6] To this end, with used the approximation $\mu_x \cong -\ln(1-q_x)$, which leads to $q_x \cong 1 - e^{-\mu_x}$.

ageing is really a constant, as we expect, all of these coefficients, except for that referred to age, should not differ significantly from zero.

4. The evolution of adult mortality

We tested our models, separately for males and females, on the cohort mortality rates of five northern European countries (Denmark, Finland, the Netherlands, Norway, and Sweden), taken from the HMD (Human Mortality Database). These series appeared to be the best candidates for an empirical estimation of the rate of ageing for three main reasons (Salinari and De Santis 2014):

Table 1. *Selected descriptive statistics of the series used in this analysis*

	Start	End	N decades	e_0 1820-9	e_0 1850-9	e_0 1880-9
Females						
Denmark	1820	1899	8	-	46.6	53.0
Finland	1850	1899	5	-	.	46.1
Netherland	1820	1899	8	-	41.0	50.5
Norway	1820	1899	8	-	52.3	55.3
Sweden	1820	1899	8	47.9	48.3	54.7
Total			37			
Males						
Denmark	1820	1899	8	-	44.6	51.9
Finland	1850	1899	5	-	.	40.5
Netherland	1820	1899	8	-	39.0	47.5
Norway	1820	1899	8	-	49.5	51.8
Sweden	1820	1899	8	43.0	45.0	51.8
Total			37			

Note: Start and End indicate the temporal extension of the cohort mortality rates series. Life expectancy (e_0) has been derived from the life tables series (lt) of the HMD, which start somewhat later than the death rates series (cMx). For the period 1820-9 only the Swedish life tables are available in the HMD.

Table 2. *Characteristics of the EGG model using five different CDF's (in decreasing order of likelihood). Initial age for the analysis: 30 years. Average parameter estimates across all the countries and all the cohorts of Table 1.*

Males	**LL**	**Initial mortality (per thousand)**	**Acc. onset (age)**	**Dec. Onset (age)**	**q_110**
Lognormal	-932,048	6.5	39.5	76.6	0.499
Inverse Gaussian	-932,061	6.8	39.2	77.8	0.511
Normal	-932,064	5.8	23.1	76.2	0.520
Gamma	-932,066	6.5	35.8	75.8	0.505
Weibull	-932,095	5.8	30.3	77.0	0.425
Females					
Lognormal	-991,911	7.2	44.7	74.4	0.494
Inverse Gaussian	-991,945	7.1	44.6	75.6	0,378
Gamma	-991,947	7.1	42.9	74.8	0.461
Normal	-991,955	6.8	38.7	74.5	0.598
Weibull	-992,039	6.5	36.7	87.8	0.391

Table 3. *Parameter estimates of the EGG model using five different CDF's (in decreasing order of likelihood). Initial age for the analysis: 30 years. Average of the five countries and all the cohorts of Table 1*

Males	**θ1**	**θ2**	**α**	**β**	**γ**
Lognormal	4.51	0.51	0.0065	0.105	0.083
Inverse Gaussian	90.63	470.72	0.0067	0.078	0.019
Normal	68.01	27.32	0.0058	0.060	0.001
Gamma	7.82	0.099	0.0065	0.070	0.074
Weibull	2.88	92.97	0.0058	0.084	-0.001
Females					
Lognormal	4.27	0.29	0.0072	0.0547	0.051
Inverse Gaussian	79.81	756.73	0.0071	0.0641	0.030
Gamma	13.07	0.14	0.0071	0.0530	0.052
Normal	67.38	17.42	0.0068	0.0460	0.014
Weibull	4.05	77.64	0.0065	0.0571	0.067

- the series were long enough for our purposes;
- the original data presented no open class (or, if yes, only at very old ages, 99 years and over);
- the perturbation produced by the two World Wars were comparatively less important than for other countries (for instance, France).

The series start in 1820 in all countries analysed except for Finland where it starts in 1850. Table 1 provides a description of the data we used for our analysis.

The variability of e_0 (cohort life expectancy at birth) is not negligible. In Sweden, for instance, life expectancy for women increased from 47.9 years in the 1820s to 54.7 in the 1880s, and the improvement was even greater for men, from 43.0 to 51.8. For both genders and in all the five countries, the improvement was particularly strong among the cohorts born in the 1870s or later. Finland lagged behind: in the 1880s, the cohorts born here lived considerably less than their Swedish counterparts: about 7 years for females, and as much as 11 years for males.

To obtain more robust estimates we worked on groups of ten non-overlapping birth cohorts, as follows

[1820-29], [1830-39], …, [1890-1899].

We therefore produced 37 estimates for each gender (74 in all) for each of the five models that we intended to compare (Table 1).

Table 2-3 shows the average results of our estimates separately for males and females, choosing 30 years as the initial age for our analysis. The log-likelihoods that appear in the table are the means of the 37 estimates, separately by gender. We used these log-likelihoods to compare the goodness of fit of the five CDF's that we considered as possible candidates for the age schedule of the rate of ageing. For both genders, the ranking was practically the same, and the lognormal distribution systematically produced the best fit.[7]

Independently of the choice of the CDF, mortality acceleration emerged earlier among males with both 30 and 50 years as the initial age for the analysis. In the former case, the EGG with lognormal CDF (our preferred choice) estimated the mortality acceleration onset at 39.5 and 44.7 for males and females respectively (Table 2). With a starting age of 50 years the onset of mortality acceleration was estimated at 39.4 years for males and 43.5 for females (not shown here). These results may be taken as an indication of a gender difference in

[7] This ranking and this conclusion hold also when the test is run on different age ranges, e.g., 20 to 109 and 50 to 109 (not shown here).

the ageing process. No significant differences appeared instead in the onset of mortality deceleration: for all the CDFs, with the partial exception of Weibull (which has the worst fit) and for both genders, this happened between 74 and 78 years. This result is consistent with the estimates produced by Horiouchi and Wilmoth (1998) on the Life Tables Ageing Rates (LAR) of Sweden and Japan.

As for the mortality level attained at age 110, no clear difference emerged between the various CDF's, again with the exception of the Weibull distribution, which led to a lower value. In the model employing the lognormal distribution (our preferred choice; Table 2) for instance, this value was 0.494 for females and 0.499 for males. Both are not far from Gampe's (2010) estimate of about 0.5.

Figures 2-3 present the results obtained for Sweden[8] with what we deem is the best model: EGG with an underlying lognormal CDF (best fit). The data (points) represent the evolution of the force of mortality from age 20 to a maximum age of 109 in the male and female Swedish cohorts born between 1820 and 1899. The models (lines), however, were estimated only on the ages between 30 and 109 (solid line), and between 50 and 109 (dotted line). The two vertical lines in each panel of Figures 2-3 represent our estimates of the onset of mortality acceleration and deceleration (for the sake of simplicity, these lines are shown only for the model estimated starting at 30 years).

From age 30 onwards, the fit is always very good in all the groups of cohorts considered, and in some cases, especially for the most recent cohorts, the fit is very good even at younger ages, from 20 years. This improvement is probably due to the progressive decrease in age of the youth mortality hump in these cohorts (Goldstein 2011).

In Figure 4 we also present the results obtained by fitting the EGG model on the Swedish period (cross-sectional) data. Period data merge the mortality of (about) 110 cohorts born t years before ($0 \leq t \leq 109$), each observed at age t: they are highly heterogeneous and are therefore particularly unfit for this kind of analysis. Still, as Figure 4 shows, the EGG model provided good results even in this case.

Back to our main line of reasoning, Figure 5 presents a disaggregation of the main features of adult mortality by gender, year of birth and country of residence as they emerged from our preferred model (initial age for the analysis set at 30 years). In all the countries and for both genders, mortality at age 30 (the starting point of our analysis) progressively declined in the 19th century, from about 8-10 per thousand in the first cohorts (1820-29) to about 4 per thousand in the last ones (1890-99), with no significant difference by gender.[9] This decline shifted the mortality hazard function downward, as Figures 2 and 3 show.

As for the onset of mortality acceleration, both male and female cohorts showed a slight decline. The causes of this anticipation are still unclear (Salinari and De Santis 2015), but they are probably connected to similar processes occurring in the age at minimum mortality which declined from 14-15 years in the past to 8-9 years in current populations, or the age when the male mortality hump is most noticeable, which, according to Goldstein (2011), declined from 24 to 18 years.

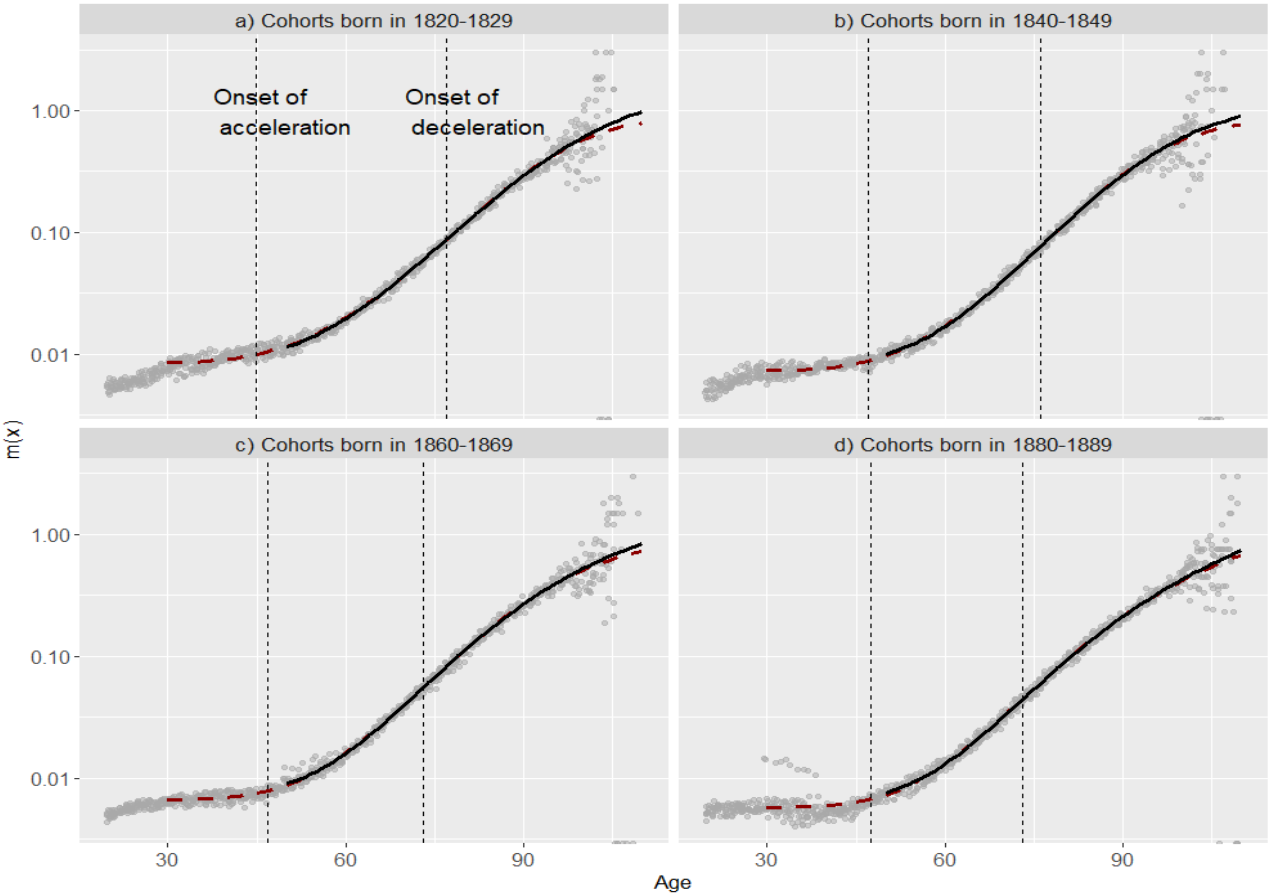
Some important differences between males and females emerge instead if we look at the onset of mortality deceleration. For women, the beginning of mortality deceleration remained remarkably stable in these birth cohorts, and close to 75 years. Among males, instead, the beginning of mortality deceleration declined from 80 to 70 years. Once again, we ignore the causes of this decrease: perhaps the spreading of some behavioural risk factors such as alcoholism and smoking, which, incidentally, would be consistent with the diverging trends observed between males and females (Pampel 2010) and with the overall timing of the process (Preston 1970; Valkonen and Van Poppel 1997).

[8] Presented as an example. Similar results can be obtained for other countries (not shown here).

[9] The higher accident-related mortality generally experienced by males has probably been compensated, along the 19th century, by a still not negligible maternal mortality in women (Loudon 1988).

The last characteristic of adult mortality presented in Figure 5 is the yearly probability of death at 110 years (initial age for the analysis set at 30 years), which did not show any systematic temporal trend among the cohorts born the 19th century, consistently with Gampe's (2010) finding[10]. In order to test the constancy of asymptotic mortality over time (i.e., mortality at very high ages) we regressed the estimated values (showed in panel (d) of Figure 5) against the year of birth of the cohorts: for both males and females, the slope of the regression line did not differ significantly from zero (p.value > 0.1).

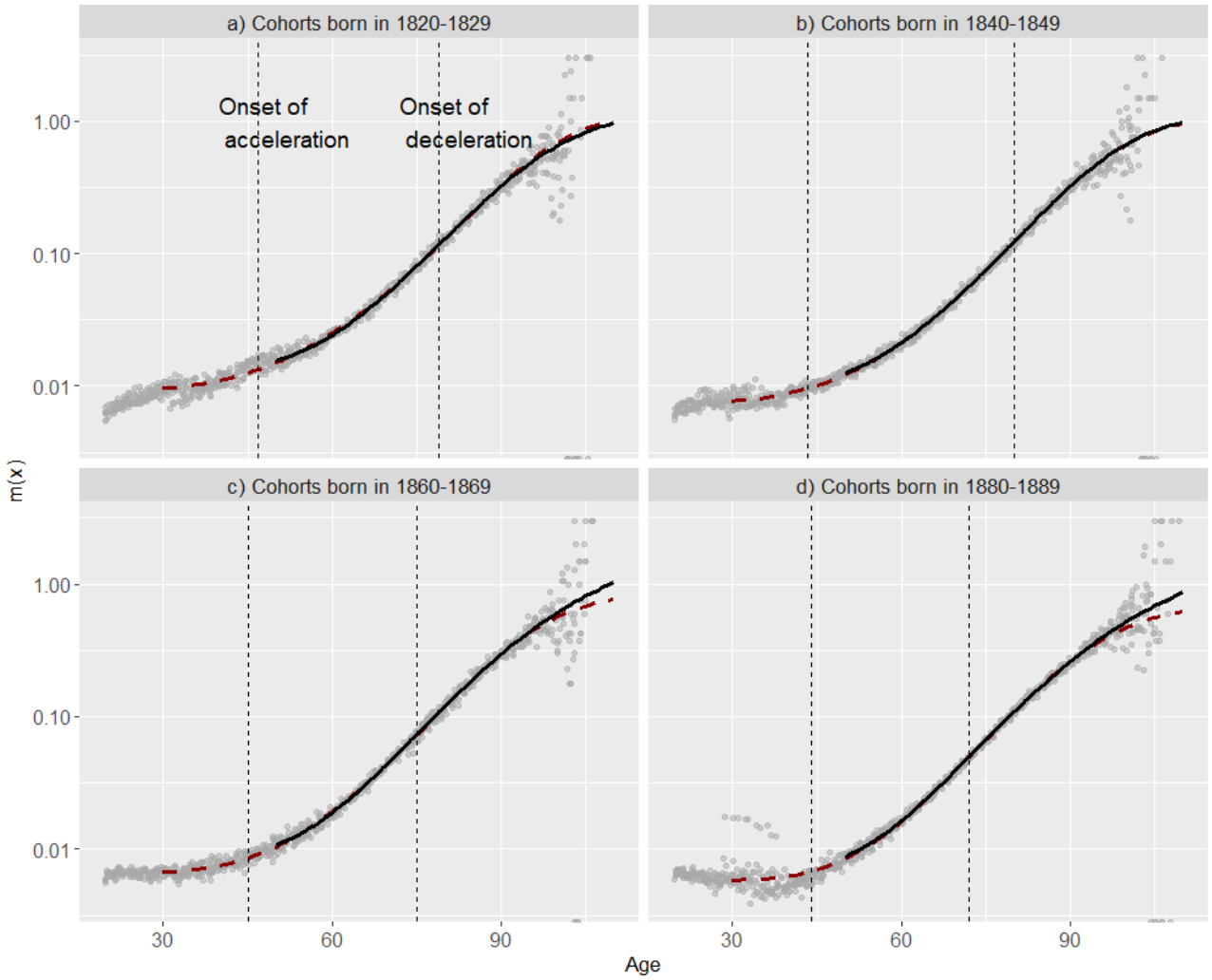
Figure 2. *Fitting the log force of mortality in selected Swedish female cohorts with the EGG, or extended gamma-Gompertz, model, assuming a lognormal CDF (cumulative distribution function)*



Note: The dashed and the solid lines indicate the EGG models obtained with a starting age of 30 and 50 years respectively. The vertical lines indicate the onset of mortality acceleration and deceleration when the analysis starts at 30 years. With a starting age of 30 years the mean squared errors (MSE) are: $MSE_{(30)1820}$=0.039, $MSE_{(30)1840}$=0.025, $MSE_{(30)1860}$=0.012, and $MSE_{(30)1880}$=0.002. When the analysis starts at 50 years, we get $MSE_{(50)1820}$=0.031, $MSE_{(50)1840}$=0.033, $MSE_{(50)1860}$=0.016, and $MSE_{(50)1880}$=0.003.

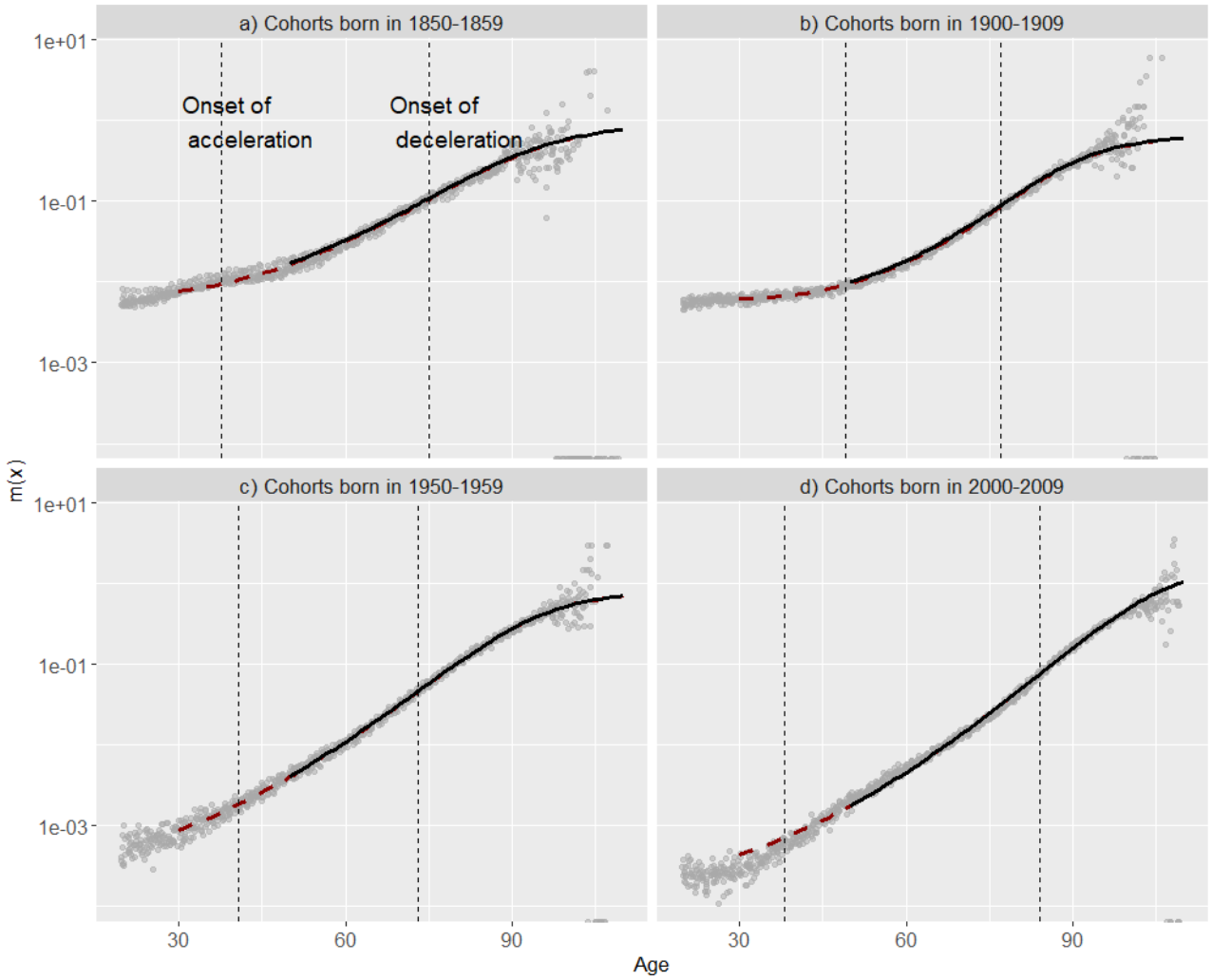
[10] Readers may notice that several q_{110} in Figure 5 have a value of about 0.66. This does not depend on a constraint imposed on our estimates (there is none, in fact). Most likely, it depends on some stiffness in the numerical optimization of the likelihood, which is hardly surprising, as the optimization takes place in a 6-dimensional space. Besides, a probability of death of about 0.66 corresponds to a mortality rate of about 1. Figure 3 and 4 show that this is a reasonable approximation for the mortality rate at age 110.

Figure 3. *Fitting the log force of mortality in selected Swedish male cohorts with the EGG, or extended gamma-Gompertz, model, assuming a lognormal CDF (cumulative distribution function)*



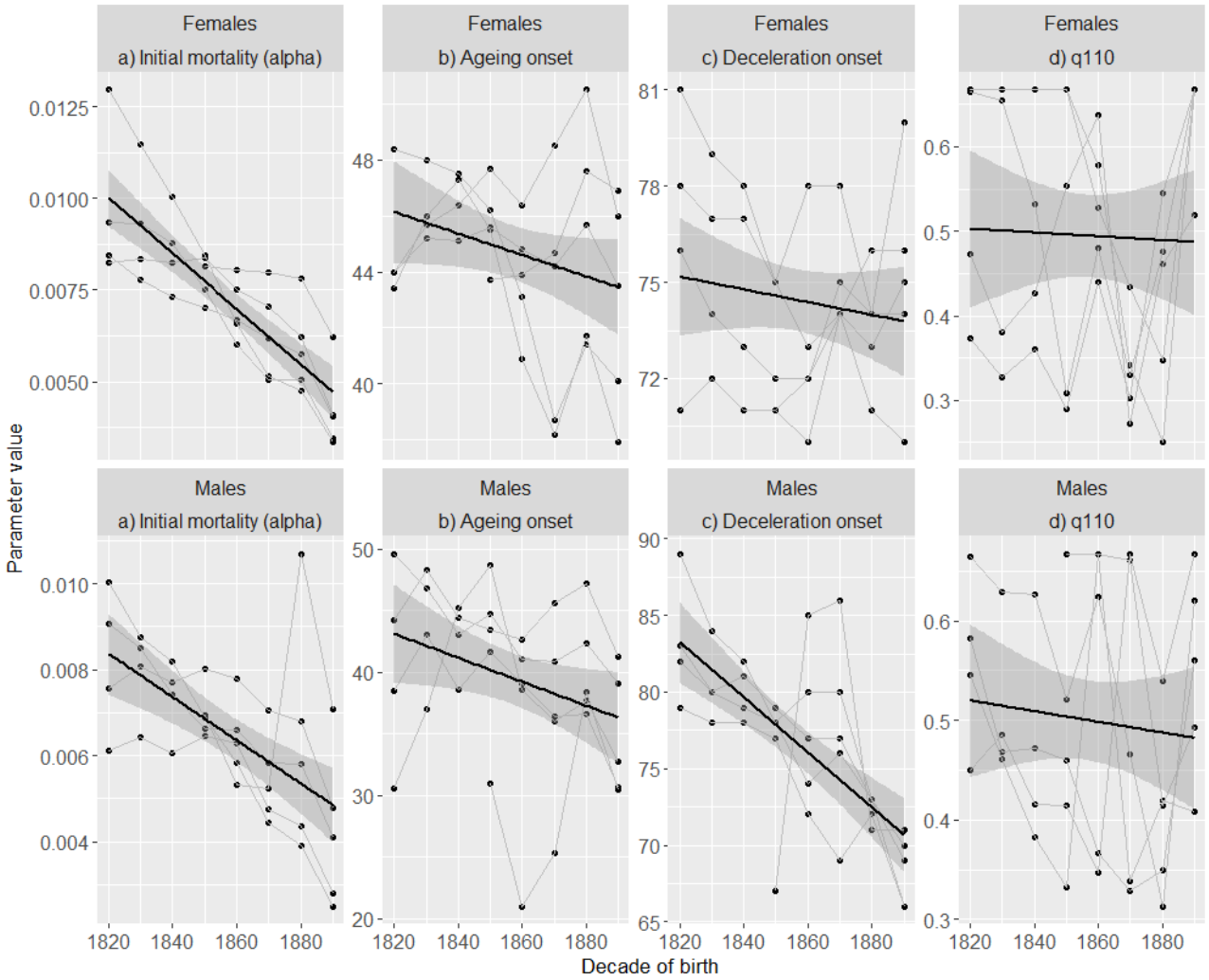
Note: The dashed and the solid lines indicate the EGG models obtained with a starting age of 30 and 50 years respectively. The vertical lines indicate the onset of mortality acceleration and deceleration when the analysis starts at 30 years. With a starting age of 30 years the mean squared errors (MSE) are: $MSE_{(30)1820}$=0.045, $MSE_{(30)1840}$=0.032, $MSE_{(30)1860}$=0.030, and $MSE_{(30)1880}$=0.017. When the analysis starts at 50 years, we get $MSE_{(50)1820}$=0.063, $MSE_{(50)1840}$=0.043, $MSE_{(50)1860}$=0.038, and $MSE_{(50)1880}$=0.022.

Figure 4. *Fitting the log force of mortality on* period *data in selected years with the EGG model (assuming a lognormal CDF). Swedish women, 1850-59 to 2000-09*



Note: The dashed and the solid lines indicate the EGG models obtained with a starting age of 30 and 50 years respectively. The vertical lines indicate the onset of mortality acceleration and deceleration when the analysis starts at 30 years. With a starting age of 30 years the mean squared errors (MSE) are: $MSE_{(30)1820}$=0.076, $MSE_{(30)1840}$=0.079, $MSE_{(30)1860}$=0.026, and $MSE_{(30)1880}$=0.001. When the analysis starts at 50 years, we get $MSE_{(50)1820}$=0.087, $MSE_{(50)1840}$=0.086, $MSE_{(50)1860}$=0.032, and $MSE_{(50)1880}$=0.003.

Figure 5. *Evolution of some characteristics of adult mortality according to the EGG model (assuming a lognormal CDF) by country, year of birth and gender*



Note: These estimates have been produced using an initial age for the analysis of 30 years. Grey lines identify country series, while the black line displays the general (linear) trend over time. The grey area gives the 95% confidence interval. This figure may be compared to Figure 10, in the appendix, where the analysis starts at age 50.

5. The evolution of the rate of ageing

With the Gamma-Gompertz model, the empirical evidence seems to reject the hypothesis of a constancy in the rate of ageing. This model, however, relies on the assumption that the rate of ageing remains constant with age, which, strictly speaking, is not a necessary condition either for Vaupel's hypothesis or for the mortality plateau at very old ages. With the EGG model, instead, we allow for an evolution of the rate of ageing with age, and Vaupel's conjecture transforms into the hypothesis that the rate of ageing remains constant at each age *x* (over time, country, gender, etc.), even if it differs by age.

In the present section, we want to check whether the shape of the hazard function described by the EGG model remains constant across time and space (see eq. 20). Contrary to what is usually done in empirical statistical analyses, our aim here is to find that, among the covariates that we include in the model, only age is statistically significant: ideally, all the others (i.e., birth cohort, country, and gender) should *not* affect the shape of the hazard function in any significant way. To ascertain whether this is really the case, we estimated

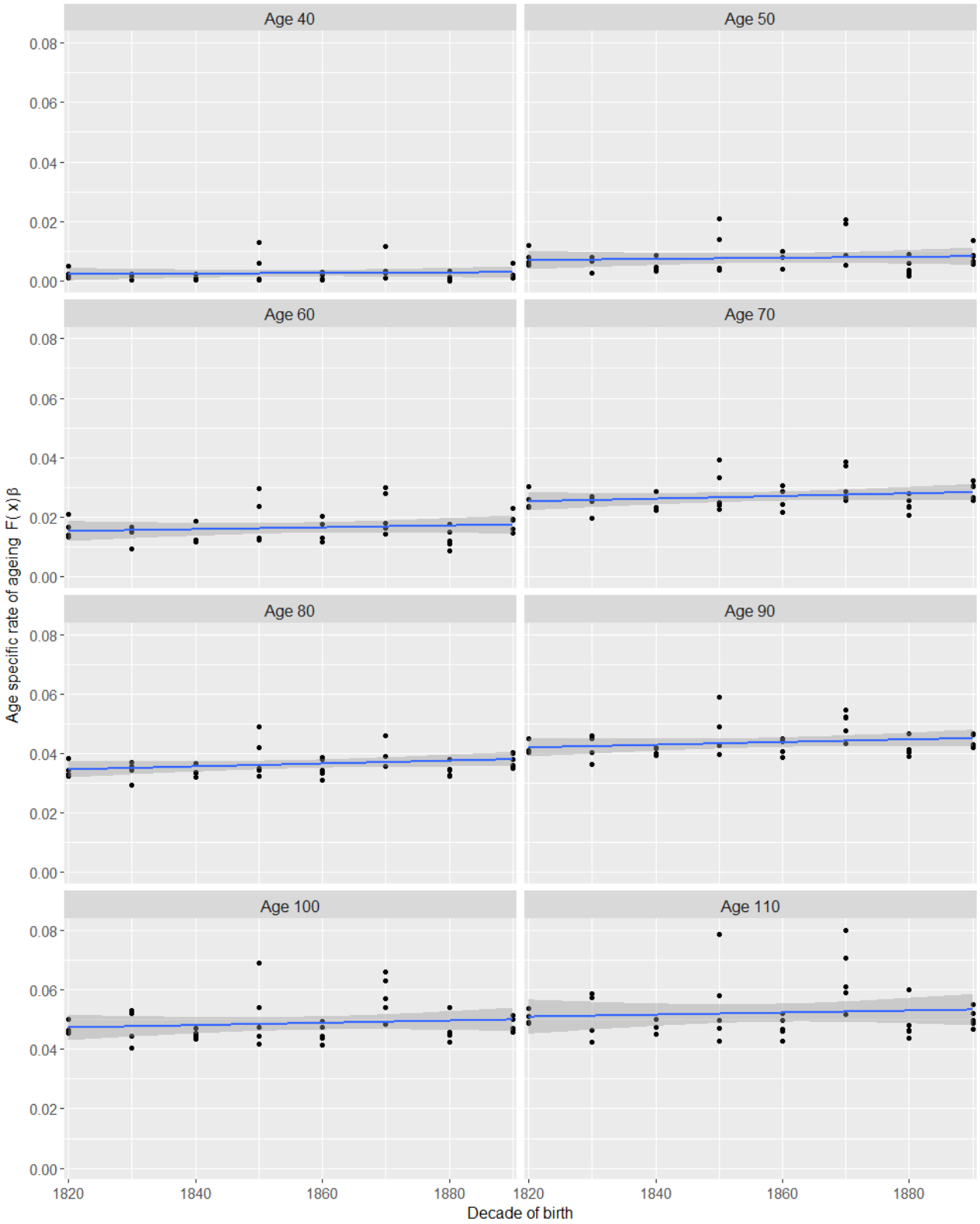
the age specific rate of ageing at selected ages (40, 50, …, 110) for each of the (37 + 37 =) 74 groups of cohorts analyzed before. And as before, we fitted our EGG model starting at two different ages: 30 and 50 years.

Perhaps the most important check about the constancy of the age-specific rates of ageing can be observed along the year-of-birth axis. Indeed, the cohorts born at the end of the 19th century were exposed during their life to mass vaccinations, sulphonamides, antibiotics, antihypertensive drugs, coronary bypass etc., while the cohorts born in the first decades of the 19th century did not experience these medical innovations, with the partial exception of vaccination. The 19th century was also a century of important changes in the nutrition and epidemiological regime. Famines, although less severe than in previous centuries, were still important in the first half of the 19th century. For instance, the Netherlands suffered two important famines in 1800 and 1816-17 (Curtis et al. 2017) and Finland was repeatedly hit by famines in 1832-33, 1857-58, 1866-68 (Dribe, Olsson and Svensson 2017). The first half of the 19th century was also affected by two important epidemics of cholera in the thirties and in the late fifties, and by an important flu epidemic. Instead, no major epidemics or famines were recorded in the last decades of the 19th century. If the shape of the individual hazard function were influenced by the changes of the epidemiological or nutrition regime, we should be able to identify them by comparing the cohorts born in the first part of the 19th century with those born in the second half of the century.

Figures 6 and 7 and Table 4 show the estimates of the age-specific rates of ageing for females and males by decade of birth (with the initial age for the analysis set at 30 years). For females, the estimates of the rate of ageing did not present any significant time trend, at any age. In the case of males, instead, a weak declining trend emerged, but only at very old ages (100 and 110 years). Globally, these trends were not significant (p.value > 0.1, Table 4). Summing up, our estimates do not show any significant evidence of the negative correlation (the so called *Strehler-Mildvan law of compensation*) between the initial mortality and the (age-specific) rate of ageing that typically emerges with the Gompertz model (Burger and Missov 2016). As for the geographic variability, among the five countries considered in this paper, only Norway presents a significantly different value with respect to our reference (Denmark). This may be due to local peculiarities (wars, epidemics, famine etc.) which, however, we did not investigate in the preparation of this paper.

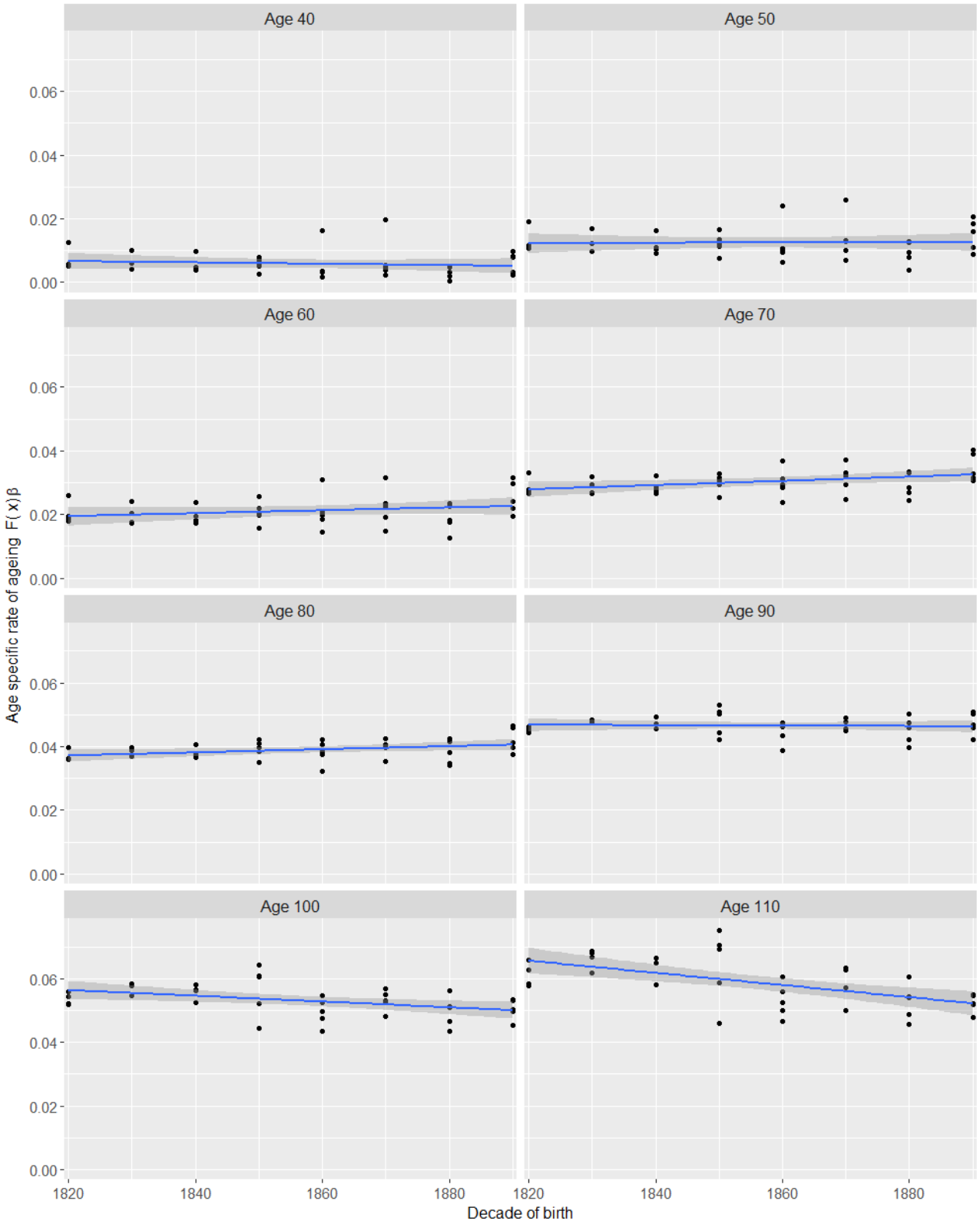
Table 4 reports also the mean age-specific rates of ageing which, as expected, turn out to be always highly significant (i.e., different from those observed at the start, 40 years).

Figure 6. Female *age-specific rate of ageing computed using the EGG model, by country (five, from Northern Europe) and decade of birth (*)*



** Indicated by its initial year: e.g., 1820=1820-29.*

Figure 7. Male *age-specific rate of ageing computed with the EGG model, by country (five, from Northern Europe) and decade of birth (*)*



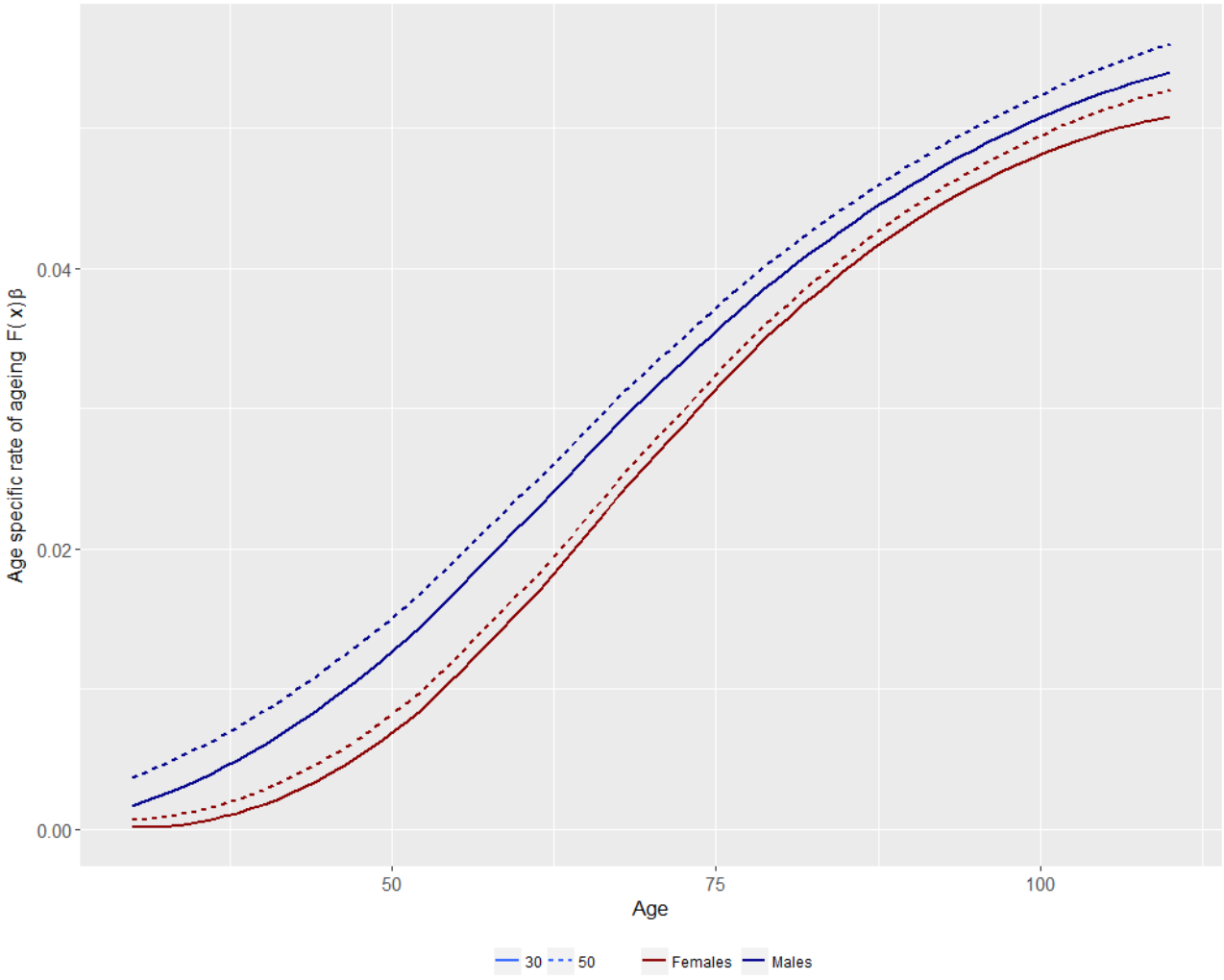
** Indicated by its initial year: e.g., 1820=1820-29.*

Table 4. Checking the constancy of the age-specific rates of ageing (estimates of eq. 20)

	Init. age 30		Init. age 50	
	Estimate	**SE**	**Estimate**	**SE**
Intercept	-2.0e-02	2.6e-02	-9.0e-02	5.2e-02
Year of birth	1.5e-05	1.4e-05	5.2e-05	2.8e-05
Gender (ref. Males)				
Females	-4.5e-03***	9.0e-04	-4.4e-03***	1.2e-03
Country (ref. Denmark)				
Finland	-2.1e-03	1.0e-0.3	2.1e-03	3.6e-03
Netherlands	-1.7e-03	1.2e-03	2.4e-03	1.8e-03
Norway	-3.7e-03**	9.7e-04	-3.4e-03*	1.3e-03
Sweden	-9.9e-04	7.7e-04	-2.1e-03	1.3e-3
Male * age (ref. 40 years)				
50	6.6e-03***	3.6e-04	6.1e-03***	3.4e-04
60	1.5e-02***	5.6e-04	1.4e-02***	5.3e-04
70	2.4e-02***	6.4e-04	2.3e-02***	6.4e-04
80	3.3e-02***	7.7e-04	3.2e-02***	7.6e-04
90	4.1e-02***	1.1e-03	4.0e-02***	1.0e-03
100	4.7e-02***	1.5e-03	4.6e-02***	1.4e-03
110	5.3e-02***	2.1e-02	5.1e-02***	1.8e-03
Female * age (ref. 40 years)				
50	4.5e-03***	3.3e-04	5.0e-03***	3.1e-04
60	1.3e-02***	5.0e-04	1.4e-02***	4.3e-04
70	2.4e-02***	4.9e-04	2.4e-02***	3.8e-4
80	3.4e-02***	4.5e-04	3.4e-02***	3.4e-04
90	4.1e-02***	5.9e-04	4.1e-02***	4.2e-04
100	4.6e-02***	8.9e-04	4.6e-02***	6.5e-04
110	4.9e-02***	1.2e-03	4.9e-02***	9.7e-04

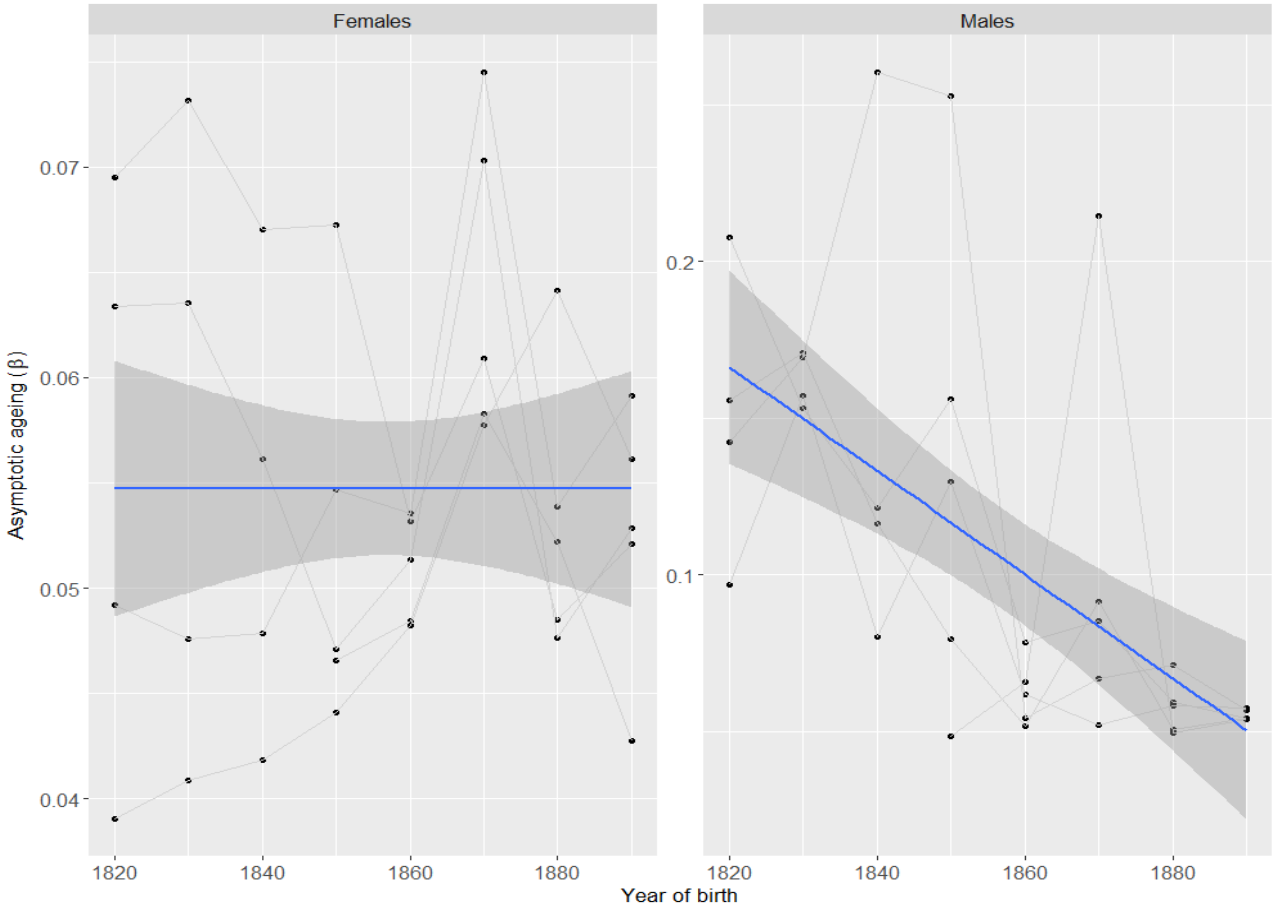
Note: Standard errors computed with the Newey-West sandwich estimator to account for heteroscedasticity.
Significance codes: * = p.value < 0.05, ** = p.value < 0.01, *** = p.value < 0.001.

Figure 8. Comparison between the mean male and female age-specific rates of ageing (all cohorts)



Note: the solid lines indicate the estimates produced with an initial age of 30 years, the dashed lines the estimates obtained with an initial age of 50 years. The red lines refer to females, while the blue lines refer to males.

Figure 9. Asymptotic ageing by country (five, from Northern Europe) and decade of birth (indicated by its start, e.g. 1820=1820-29)



A systematic difference remains between males and females. Figure 8 shows that independently of the initial age for the analysis, males age slightly faster than females. The relative distance between genders decreases with age, but it never disappears, not even at the oldest ages. This is consistent with the well-known systematic male-female differential in survival (Beltrán-Sánchez, Finch and Crimmins 2015; Colchero et al. 2016). This is also consistent with our previous finding (see section 4) that the initial mortality was slightly higher in females than in males in our 19th century cohorts, probably due to maternal mortality. If the initial level of mortality was higher among females, then higher female longevity can only be achieved by a difference in the ageing process (delayed onset of mortality acceleration or slower ageing, or both). The slower progression of ageing for females that we found in this analysis contradicts the previous estimates produced with the Gamma-Gompertz model, which had systematically found a more rapid ageing in females (Barbi 2003; Salinari and De Santis 2014) and which, we venture, may have been an artefact of the simper models used in those cases.

Finally, let us also consider the asymptotic rate of ageing (β) in Figure 9. In the case of females, the estimates make sense: the mean asymptotic rate of ageing is practically constant, on average, at about 0.055. When it comes to males, however the asymptotic rate of ageing (0.1) is far from what we found for females. Besides, the male asymptotic rate of ageing seems to have declined dramatically during the 19th century. A closer inspection of Figure 9 shows that, for males, 12 estimates (out of 37) are extremely high: this happens in the oldest cohorts, born in the early period 1820-1859, i.e. arguably with worse data (and fewer cases). If we dropped these cases, the estimates for males would become 0.061, more in line with what we found for females and with expectations.

We do not know why this problem arises in older male cohorts: perhaps the typical life span of the males born between 1820 to 1859 was too short, and the data too noisy, to allow researchers to estimate the asymptotic behaviour of ageing after 100 years. Note, incidentally, that the same data limitation affected the

Kannisto-Thatcher database on supercentenarians, which led Gampe to conjecture the existence of a mortality plateau. It contained 573 females but only 64 males, and all of these supercentenarians were born in the second half of the 19th century.

6. Conclusions

The discovery of the mortality plateau and several theoretical advances produced in the last ten to fifteen years suggest that proportional hazards are the best models to describe the evolution of mortality with age. The basic assumption of these models is that frailty and the covariates act multiplicatively on a baseline mortality hazard function. This implies that the shape of the baseline log hazard function should not change significantly across different human populations. On this basis, we tested the goodness of an extention of the gamma-Gompertz (or EGG) model, which introduces the idea that the rate of ageing increases with age before converging to its asymptotic value.

In the five countries analysed in this paper (Denmark, Finland, the Netherlands, Norway, and Sweden) survival improved significantly in the birth cohorts 1820-1899. In this, admittedly limited, analysis, the EGG model seems to confirm that the bulk of process can be described as a downward translation of the individual hazard, without major changes in its shape. In other words, the observed decline in adult mortality seems to take place mostly because of a reduction in initial mortality (α), but not because of a change in the age-specific rates of ageing ($F(x)\beta$). This result is consistent with the existence of a mortality plateau (starting somewhere between 110 and 120 years) and its mathematical implications on the shape of the underlying mortality curve.

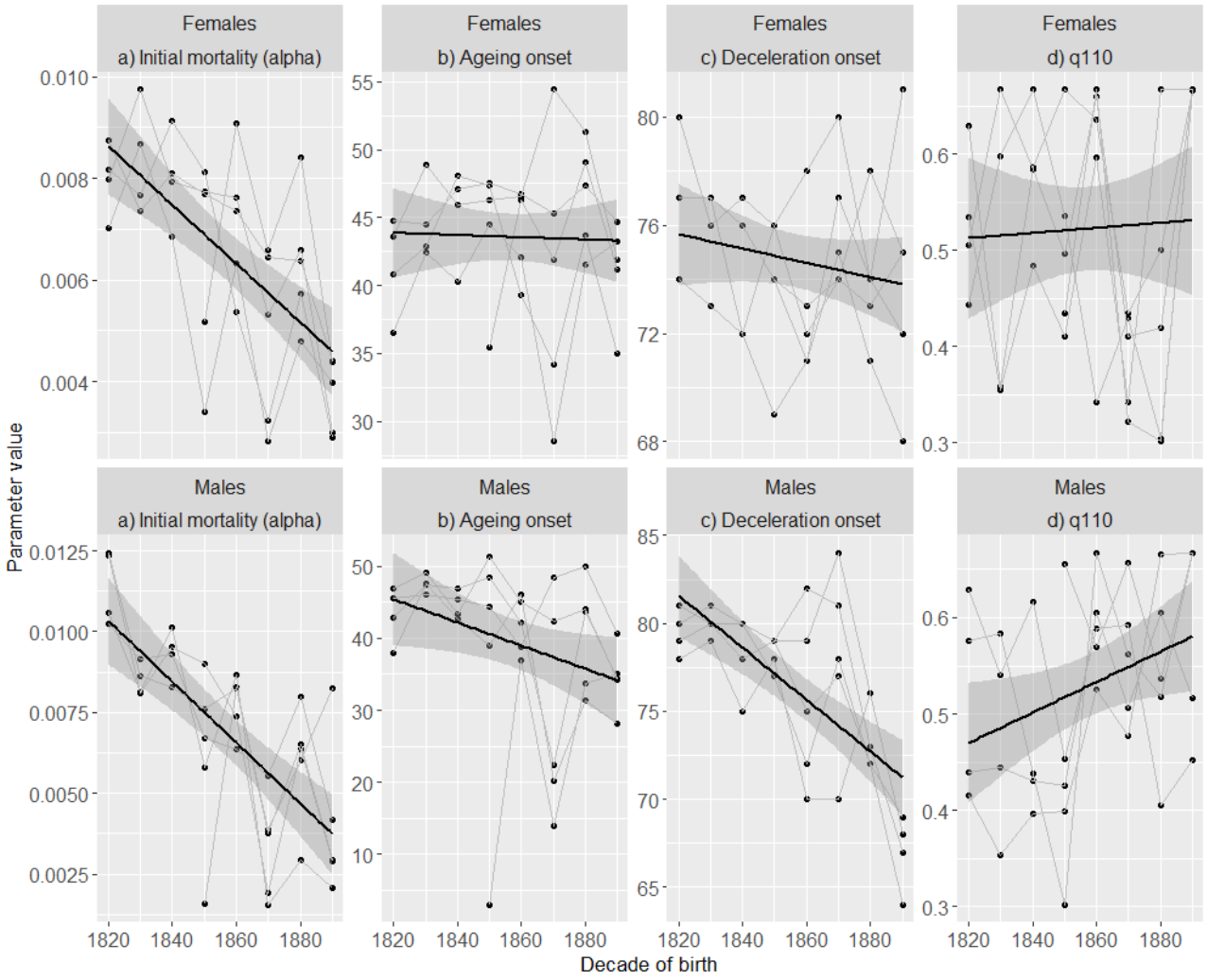
The analysis presented here must be regarded as an initial investigation on the shape of the individual hazard function. Its main goal is to show that there is an infinite class of models which extends the traditional gamma-Gompertz approach, is consistent with the formation of the mortality plateau, fits reasonably well with empirical data and which, to the best of our knowledge, had not been previously considered in the literature. Within this infinite class, we explored only a few models, mainly because of technical limitations. The implication is that we are not sure that we picked the best EGG (extended gamma-Gompertz) model: it is the best among those that we tried.

Most of the results presented here rely on the still debated existence of a mortality plateau. This plateau, however, may be the result of the very high sample variability of mortality rates at very old ages, or it may be merely a temporary phase in the evolution of human mortality. In this case, some of the conclusions that we present here may not hold.

Appendix

In this section we present the evolution of some characteristics of adult mortality according to the EGG model (assuming a lognormal CDF), by country, year of birth and gender (Figure 10). Differently from the estimates presented in Figure 5 in the main text, the estimates of Figure 10 have been produced using an initial age of 50 years.

Figure 10. *Evolution of some characteristics of adult mortality according to the EGG model (assuming a lognormal CDF) by country, year of birth and gender*



Note: These estimates differ from those of Figure 5 in the age when the analysis starts: it was 30 years in Figure 5, it is 50 years here. The grey lines identify country series. The black line indicates the general (linear) trend over time. The grey area gives the 95% confidence interval.

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