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Demographic Consequences of Barker Frailty

Alberto Palloni* Hiram Beltrán-Sánchez†

Abstract

In this paper we develop a formal model to represent effects of early life conditions with delayed health impacts on old age mortality. The model captures several mechanisms through which early conditions influence adult health and mortality. The model is an extension of the standard frailty model in demographic analysis but has distinct and unique implications. We show that populations with Barker frailty experience adult mortality patterns equivalent to a class of time-varying and/or age dependent frailty. We demonstrate formally and via simulations that populations with Barker frailty could experience unchanging or increasing adult mortality even when background mortality has been declining for long periods of time. We also show that the rate of increase of adult mortality rates in populations with Barker frailty will change over time and will always be lower that the rate of increase of adult mortality in the background mortality pattern. We argue that Barker frailty should be pervasive in low-to-middle income populations, e.g. those that experienced a mortality decline fueled largely by post-1950 medical innovations that reduced the load and lethality of infectious and parasitic diseases.

Key Words: Barker hypothesis, Old age mortality, Demographic frailty

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1 Introduction

In this paper we develop a formal model to represent the effects of early life conditions with delayed health impacts on patterns of old age mortality. The model can capture three types of mechanisms: those involving exposure to early malnutrition and deprivation (Barker, 1998; Gluckman and Hanson, 2006; Langley-Evans, 2004), those linking early infectious diseases and adult chronic conditions (Elo and Preston, 1992; Fong, 2000) and, finally, those working through sustained inflammation to promote adult chronic illnesses (Finch, 2007; Finch and Crimmins, 2004; Crimmins and Finch, 2006; Danesh et al., 2000; McDade et al., 2010). In our model the excess mortality implications of these processes are identical and we use the term 'Barker frailty' to refer to each one of them, all of them, or specific combinations including some of them[1]. The formal model is an extension of the standard frailty model in demographic analysis (Vaupel et al., 1979; Vaupel and Yashin, 1987; Vaupel and Missov, 2014; Manton et al., 1986; Hougaard, 1986; Steinsaltz and Wachter, 2006; Aalen, 1988). We show that adult mortality patterns in populations with Barker frailty are equivalent to adult mortality patterns in populations with a class of time-varying and/or age dependent frailty. We demonstrate formally and via simulations that populations with Barker frailty could, in theory at least, experience unchanging or increasing adult mortality even when background mortality has been declining for long periods of time. Most commonly, however, these populations will experience slower rates of mortality decline than the background mortality regime. We argue that Barker frailty should be pervasive in low-to-middle income populations, e.g. those that experienced a mortality decline fueled largely by post-1950 medical innovations that reduced the load and lethality of infectious and parasitic diseases.

The plan of the paper is as follows: in section 2 we define the theoretical underpinnings of the notion of Barker frailty; in Section 3 we propose alternative models to formalize Barker frailty and Barker effects; in section 4 we develop generalized models better suited for capturing dynamics associated with changes in the size and/or heterogeneity of populations expressing Barker frailty; in section 5 we introduce simulations to assess the impact of Barker frailty on adult mortality rates and review selected results. The last section summarizes findings, discusses implications, proposes extensions of the model, and concludes.

2 Nature of Barker frailty

There is solid empirical evidence and persuasive theoretical argumentation supporting the idea that early life conditions–*in utero*, around birth and during early childhood–exert an important influence on adult health and mortality (Barker, 1998; Anson, 2002; Gluckman and Hanson, 2006; McDade and Kuzawa, 2004; Langley-Evans, 2004; Beltrán-Sánchez et al., 2012; Barouki et al., 2012). The mechanisms that trigger these delayed effects involve redirection of processes of organ-specific cell growth and functional differentiation, various types of epigenetic changes (histone covalent modifications, non-coding RNA expression, methylation) manifesting developmental plasticity, and more general conditions including exposure

[1]Our model is a particular case of a more general representation that includes all the nuances associated with each of these three mechanisms.

to acute poverty, deprivation, and stress (Forsdahl, 1977, 1978). The best known, albeit not the most comprehensive, version of the hypothesis of delayed health effects, was articulated by Barker (Barker, 1998). The cornerstone idea of this variant of the theory ('fetal programming') is that nutritional deprivation *in utero*, and soon after birth, disrupts processes of organ formation (cell division, cell growth and functional specialization) and exposes survivors to excess risk of developing a number of chronic conditions during late adulthood, including type-2 diabetes *mellitus* (T2D), hypertension and other circulatory disorders, kidney and heart disease, and some diseases of the respiratory system.

An older, related, but better established strand of the literature identifies linkages between exposure and contraction of specific early life infections and the development of adult chronic conditions. Examples of this mechanism include the relation between *helicobacter pylori* and colon cancer, HPV and uterine cancer, *Hepatitis B* and liver cirrhosis and cancer, and rheumatic heart fever and mitral valve stenosis. In all these cases exposure and contraction of well-defined infections induces organ damage manifested in adult chronic illnesses (Fong, 2000; Elo and Preston, 1992).

Finally, a third mechanism linking early conditions and adult health via delayed response involves sustained inflammation that results from recurrent episodes of infectious diseases, persistent and durable but low-level infections and, more generally, continuous exposure to multiple infectious and parasitic diseases (Finch, 2007; Finch and Crimmins, 2004; Crimmins and Finch, 2006; Danesh et al., 2000). The theory suggests that when the inflammatory processes promoted by these exposures are long lasting, such as those associated with *periodontitis* or *chlamydia pneumoniae* (Fong, 2000) they are likely to generate physiological damage that increases susceptibility to chronic illnesses (Finch, 2007).

A common theme of all three mechanisms identified above is the presence of organ damage or abnormal immune/metabolic responses triggered by adverse early experiences, long latency periods, and delayed manifestations in late adulthood. The expression of the damage inflicted early in life is observable only if the following conditions are met: (a) members of a birth cohort who experience the offending early conditions survive beyond some critical age Y_1 after which manifestation of the original damage begins to unfold; (b) the delayed effect must be significant in the sense that it should implicate a broad range of illnesses and conditions with high fatality rates; (c) the beneficial mortality-related effects of medical technological advances adopted and diffused between the time of onset of adverse experiences and the time at which the birth cohort attains the critical age Y_1 are less than the excess mortality risks implied by chronic conditions related to Barker frailty.

In a population that meets all the foregoing conditions, time trends of adult mortality may experience singular features. In a secular mortality decline, the rate of mortality reduction over time will slow-down (at all ages), even if the background rate of mortality decline remains invariant. This should always occur when the mortality regime is influenced by standard frailty. When, in addition, Barker frailty and effects are present, the rate of mortality decline at ages above Y_1 can decrease, converge to zero or even increase. In an unchanging mortality regime the impact of Barker frailty on adult mortality rates crucially depends on the fraction of individuals who experience early damage and survive past age Y_1. Two invariant mortality regimes with identical mortality rates above age Y_1 but different

survival probabilities to age Y_1 could result from very different Barker frailty dynamics, none of which is identifiable from conventionally available data. By contrast, mortality regimes affected by a secular decline offer an opportunity to identify the imprints of Barker frailty. In fact, when reductions in mortality are partially or totally sustained by massive improvements in infant and child survival there will be potentially large but lagged increases of the fraction of individuals surviving to ages past Y_1. This opens the gates for expression of Barker frailty. Declining mortality regimes such as those that emerged after 1950 in low-to-middle income countries are enablers of Barker frailty and, as a result, mortality trajectories may undergo stages in which adult mortality rates decline more slowly than background mortality rates, remain steady, or even increase.

In a mortality regime with declining mortality the selection pressure of standard frailty on members of a cohort weakens over time. When this is combined with Barker frailty the levels of adult mortality will be subject to two sources of upward pressure: the first is rooted in the increase of (standard) mean frailty of individuals who attain adult ages, a natural product of mortality decline. The second originates in excess mortality risks shared by at least a fraction of 'new' survivors who were exposed to adverse early life conditions and who attain adult ages in the lower mortality regime. Thus, Barker frailty will magnify the decelerating force that naturally arises when only standard frailty prevails.

Although we do not explore them in this paper, the presence of Barker frailty leads to predictions for aggregate outcomes (rate of mortality change, slope of adult mortality) that could be tested with empirically observed patterns to identify some of the mechanisms described above.

3 Formal models for Barker frailty and Barker effects

To fix concepts and set up notation we begin with a brief review of the standard frailty model in continuous and discrete form. We then introduce a general form of the model, continuous and discrete versions, and variants using the Gamma distribution.

3.1 Standard frailty: continuous and discrete models

The standard frailty model assumes the existence of an age-invariant trait ε assigned to individuals at birth according to some known probability distribution. The role of this trait is to shift individual mortality levels by the same amount at all ages. Although the interpretation of the trait is the subject of some controversy, in most cases it is assumed to refer to some fixed, perhaps genetic, endowment and not to an acquired one (Vaupel et al., 1979; Vaupel and Missov, 2014; Vaupel and Yashin, 1987; Kannisto, 1994; Aalen, 1988; Hougaard, 1986; Manton et al., 1986).

Let $\mu_i(y)$ represent the force of mortality at age y for individual i, $\mu_s(y)$ be a baseline mortality rate, and $\bar{\mu}(y)$ the average mortality rate at age y . The standard frailty model is fully defined by a pair of related equations:

$$\begin{aligned} \mu_i(y) &= \varepsilon_i \mu_s(y) \\ \bar{\mu}(y) &= E_y(\varepsilon)\mu_s(y) \end{aligned} \tag{3.1}$$

where ε_i is random frailty with density $f(\epsilon)$. The expected value of the frailty trait at age y under density $f(\varepsilon)$, $E_y(\varepsilon)$, depends on the conditional density of the trait at age y and this, in turn, is a function of probabilities of surviving to age y. The key insight is that the population composition by trait ε changes as mortality differentially selects out individuals with higher values of ε. In particular, the slope of average mortality rates should increase less rapidly than the slope of the baseline mortality rates.

A very special case of (3.1) is when ε attains only one of two values, say $\varepsilon_1 > \varepsilon_2$ with probabilities f and $(1-f)$ and the average force of mortality is

$$\bar{\mu}(y) = \left[\varepsilon_1 \left(\frac{1}{1 + h\, exp(-(\varepsilon_2 - \varepsilon_1)\Lambda_s(0,y))}\right) + \varepsilon_2 \left(\frac{h\, exp(-(\varepsilon_2 - \varepsilon_1)\Lambda_s(0,y))}{1 + h\, exp(-(\varepsilon_2 - \varepsilon_1)\Lambda_s(0,y))}\right)\right] \mu_s(y) \tag{3.2}$$

where $h = (1-f)/f$ and $\Lambda_s(0,y) = \int_0^y \mu_s(x)dx$). Because $\varepsilon_1 > \varepsilon_2$, the average mortality rate will always be closer to mortality rates among those with frailty ε_2 (Vaupel and Yashin, 1987).

3.2 Barker frailty: general continuous model

A model for Barker frailty includes and defines two key properties. First, individuals who could express Barker frailty experience excess mortality (Barker effects) at adult ages (and perhaps in early childhood) but not necessarily in the rest of the life course. Second, the fraction of individuals at adult ages who could potentially express Barker frailty must increase whenever mortality declines. This can take place via two different but not always dependent mechanisms. The first operates by simply reducing selective pressure: individuals who would have died in a higher mortality regime can survive to adult ages in a more beneficial regime and some of them may be carriers of Barker frailty. The second mechanism increases the fraction of births that are carriers of Barker frailty and, therefore, augments the pool of individuals who can potentially express Barker frailty, irrespective of mortality changes. This mechanism operates when there are improvements associated with mortality decline, such as reduced maternal exposure to parasitic and infectious diseases and better prenatal care, that translate into lower fetal and perinatal mortality rates. These mechanisms can prevail alone or in combination and the models below offer room to incorporate either of them.

3.2.1 Barker frailty and Barker effects with unchanging mortality

The simplest model assumes the existence of a trait, δ, acquired as early as during conception and gestation that continues to be shaped during early childhood. Thus, in theory at least, the trait itself can be changing at least for some time before full adulthood. Once the trait is shaped and its value fixed, it will mark individual carriers throughout life. As in the standard frailty model, the effects of the trait on mortality rates will be multiplicative but could vary with age.

We introduce the function $R(\delta, y)$ to reflect the impact of Barker frailty on adult mortality, e.g. the Barker effect (for $y > Y_1$). A very general form is $R(\delta, y) = 1 + I_i(\alpha_1(y - Y_1) + \alpha_2(\delta - \delta_0))$ with $\alpha_1 > 0$, $\alpha_2 > 0$, and I_i a random indicator function attaining value 1 if

$\delta > \delta_0$ and 0 otherwise, where δ_0 is a threshold Barker frailty value for expression of Barker effects and for $y >$Y$_1$. The force of mortality of individual i is

$$\mu_i(y) = \mu_s(y)\{\delta_i(1 - I_i) + \delta_i[1 + I_i(\alpha_1(y - Y_1) + \alpha_2(\delta_i - \delta_0))]\}, \quad \forall\, y > Y_1 \tag{3.3}$$

and the average mortality rate at age $y > Y_1$ is

$$\bar{\mu}(y) = \frac{\mu_s(y)[E_y(\delta|\delta > \delta_0)(1 + (\alpha_1(y - Y_1)) + \alpha_2 E_y(\delta(\delta - \delta_0)|\delta > \delta_0) + E_y(\delta|\delta \leq \delta_0)D_y]}{1 + D_y} \tag{3.4}$$

where D$_y$ is a function of the baseline survival from 0 to y and the expected value of the probability of surviving to age y among those with $\delta > \delta_0$

Expression (3.4) contains the contributions of two subpopulations to excess mortality relative to the baseline: the first is associated with the subpopulation that meets the condition $\delta > \delta_0$, namely, $(E_y(\delta|\delta > \delta_0)(1 + (\alpha_1(y - Y_1)) + \alpha_2 E_y(\delta(\delta - \delta_0)|\delta > \delta_0))$, and the second is associated with the subpopulation that does expresses only standard frailty, namely, $E_y(\delta|\delta \leq \delta_0)$. The first part includes the influence of standard frailty, the effect of age ($\alpha_1' s$), and of excess triggered by the level of individual frailty ($\alpha_2' s$). As is the case of standard frailty, the expected value of the force of mortality is an implicit function of the integrated hazards up to age y that contribute to the moments of the conditional distribution of δ and embedded in D_1. Unlike the case of standard frailty, equation (5) involves the first as well as second moments of the conditional distribution for all ages above Y_1.

The expression in (3.3) captures a number of desirable features identified above. First, Barker frailty is a random trait acquired early in life and influencing mortality at all ages. Second, there is a critical age Y_1 above which Barker frailty expresses itself as excess mortality risks (Barker effects). Third, the excess mortality risk can potentially increase after attaining the critical age Y_1 and could do so as a function of the individual level of Barker frailty. The latter feature implies that survivors at older ages who express Barker frailty will do so in direct proportion to their level of vulnerability.

Note that, at the outset, the model above (3.3) imposes the restriction that the critical age, Y$_1$, is a fixed quantity. This need not be the case. It is conceivable that the critical age itself is a function of individual experiences or traits as well as of features of the background epidemiological regime. To reflect this we could extend the model so that Y_1 is also a randomly distributed trait with a systematic component associated with background mortality. Because this extension complicates the model and obscures its main features we pursue the generalization elsewhere. In a comparative statics exercise (section 5.4), our simulations show that variation in the threshold age Y_1 has considerable impact on the slope of average mortality rates and on average levels of Barker frailty.

3.2.2 Barker frailty and Barker effects with secular mortality decline

Introducing generalized Barker frailty as in (3.3) when the mortality regime is changing complicates the algebra. To simplify developments we will assume $\alpha_1 = \alpha_2 = 0$ and $\alpha_0 = R > 1$. Although less rich, this formulation enables us to identify the main properties of Barker

frailty and minimizes clutter without great loss of generality[2]. In this simpler formulation the average mortality level at age y is given by

$$\bar{\mu}(y) = R(y)E_y(\delta)\mu_s(y) \tag{3.5}$$

where, for simplicity, $R(y) = R$ for $y \geq Y_1$ and $R(y) = 1$ otherwise[3]. The survival function to age $y \geq Y_1$ for individual i that is implicit in (3.5) is given by

$$\begin{aligned} S_i(y) &= exp\left(-\delta_i\left(\int_0^{Y_1}\mu_s(x)dx + R\int_{Y_1}^{y}\mu_s(x)dx\right)\right) \\ &= exp\left(-\delta_i\Lambda_{sB}(y)\right) \end{aligned} \tag{3.6}$$

where $\Lambda_{sB}(y)=\int_0^{Y_1}\mu_s(x)dx+R\int_{Y_1}^{y}\mu_s(x)dx$ is the integrated force of standard mortality from age 0 to age y with Barker effects. In this variant of the model, the *cumulated* Barker effects reflected on the integrated force of mortality to any age $y \geq Y_1$ are larger when R increases and when the critical age Y_1 decreases.

Assume now that the mortality regime undergoes a secular change with onset at $t = 0$ and that each birth cohort is exposed to a mortality level corresponding to the year when they were born. Thus, members of a birth cohort born t years after the onset of the secular decline experience throughout their lives mortality rates from the life table for year t. To define each birth cohort's life table we assume there is a standard mortality pattern characterized by mortality rates $\{\mu_s(y)\}$ and that the force of mortality for year t ('background' mortality) is $\mu(y,t) = k(t) * \mu_s(y)$,where $k(t)$ is a monotonically decreasing function of time (linear or exponential)[4]. The force of mortality at age y for a member of a cohort born in year t is given by

$$\mu_i(y,t) = \begin{cases} \delta_i k(t)\mu_s(y), & \forall y \leq Y_1 \\ R\delta_i k(t)\mu_s(y), & \forall y > Y_1,\ R \geq 1 \end{cases}$$

The expression for the average mortality at any age $y \geq Y_1$ in a cohort born t years after the onset of the mortality decline is:

$$\bar{\mu}(y,t) = RE_{yt}(\delta)k(t)\mu_s(y)$$

and

$$E_{yt}(\delta) = \frac{\int_0^\infty \delta\, f(\delta)\, exp(-k(t)\delta\Lambda_{sB}(y))d\delta}{\int_0^\infty f(\delta)\, exp(-k(t)\delta\Lambda_{sB}(y))\, d\delta}$$

[2]As we show later, the simpler functional form adopted here represents lower bounds of Barker effects in the sense that time trends in both adult mortality levels and age patterns are least affected by their presence.

[3]In a recent paper Vaupel and Missov (2014) proposes an equivalent age dependent effect of standard frailty but with no association to Barker's conjecture. Coincidentally, we are using the same symbol, R, to express extra mortality in the special case when $R(\delta,y) = R(y) = R$ is constant.

[4]This simplified functional form for mortality decline avoids cumbersome algebra but leads to no loss of precision or generality.

where $f(\delta)$ is the density of Barker's frailty. The time dependency of Barker effects — $R * E_{yt}(\delta)$—is a result of changes in mortality that increase both survival probabilities and the conditional mean of Barker frailty[5].

How does the average force of mortality at age y change over time? Note that when there is neither standard nor Barker frailty the change over time of average mortality rates depends only on changes in the function that controls the secular mortality decline or background mortality. In contrast, when there is Barker frailty the derivative of the force of mortality at age $y > Y_1$ at time t depends on changes in the expected value of a time dependent function:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t} + \frac{\partial \ln(E_{yt}(\delta))}{\partial t} \tag{3.7}$$

with $\frac{\partial \ln(k(t))}{\partial t} < 0$. Since mortality is declining the time derivative of $E_{yt}(\delta)$ is positive because as time passes the fraction of a cohort that survives to age Y_1 will have higher Barker frailty (values of δ). This occurs by virtue of the mortality decline itself that allows more children and young adults with higher values of Barker frailty to survive to adult ages (see below). Thus, according to (3.7) it is possible that changes in $\bar{\mu}(x,t)$ over time can be negative, 0, or positive for some values of y and t. At the very least, though, the presence of Barker frailty will offer resistance to the rate of mortality improvements. We explore this below.

3.2.3 The nature of changes in $E_{yt}(\delta)$ and $\bar{\mu}(y,t)$

a. *Time dependent changes at ages $y > Y_1$*

When mortality declines rapidly, the derivative of $k(t)$ will be large and negative. However, because a faster mortality decline also increases more rapidly the fraction of individuals with higher levels of Barker frailty who survive to adult age Y_1, the change in $E_{yt}(\delta)$ will be larger and, consequently, the absolute value of the derivative of the second term in (3.7) will also be larger [6].

One can show that

$$\frac{\partial \ln(E_{yt}(\delta))}{\partial t} = -\frac{\partial \ln(k(t))}{\partial t}[\bar{\Lambda}(y,t)(CV_{yt}(\delta))^2] \tag{3.8}$$

where $\bar{\Lambda}(y,t) = \Lambda_{sB}(y)k(t)E_{yt}(\delta)$ is the average integrated hazard at age y for the cohort born at time t and $CV_{yt}(\delta)$ is the coefficient of variation of the conditional density δ at age y and time t. Thus, larger increases in average Barker frailty take place when the distribution of δ has higher variance and at higher levels of mortality, that is, in the earlier stages of the secular mortality decline. From (3.8) and (3.7) we get

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t}[1 - \bar{\Lambda}(y,t)(CV_{yt}(\delta))^2] \tag{3.9}$$

[5]Below we explore the case when time dependency of Barker effects is linked not to mortality decline but to changes in the distribution $f(\delta)$.

[6]Expression (3.7) also holds with standard frailty. The difference between it and the standard frailty case is in the quantities that come into play: in the case of Barker frailty the value of $\partial \ln(E_y(\delta,t))/\partial t$ depends on R (not just on δ) via the dependence of the integrated survival function on R (see equation (3.6)).

Since $\bar{\Lambda}(y,t)(CV_{yt}(\delta))^2$ can potentially attain values higher than 1, adult mortality decline could slow down, stop altogether or even reverse. Expression (3.9) is general and also applies to standard frailty. The main difference is that in the case we study here the value of $\bar{\Lambda}(y,t)$ will always be larger for ages $y > Y_1$. Since the relative magnitude of $(CV_{yt}(\delta))^2$ depends in both cases on the original and conditional, age-specific distributions of δ, the differences between effects of standard and Barker frailty cannot be determined *a priori*. If excess risks are large or Y_1 is low, the influence of the integrated hazard will dominate and the effects of Barker frailty on the average rate of mortality decline will be substantially larger than under standard frailty alone. Finally, since the variance of the conditional distribution of frailty must converge to 0 at very old ages, the rate of mortality decline will converge to the rate of background mortality decline.

b. *Age dependent changes at ages $y > Y_1$*

We now explore the influence of Barker effects on the age-related slope of average mortality rates. The first age derivative of $E_{yt}(\delta)$ is given by[7]:

$$\frac{\partial \ln(E_{yt}(\delta))}{\partial y} = -\bar{\mu}(y,t)(CV_{yt}(\delta))^2 = -RE_{yt}(\delta)k(t)\mu_s(y)(CV_{yt}(\delta))^2$$

As expected, this derivative will always be negative, that is, the mean level of Barker frailty will decrease with age and the rate of decrease will be faster in this regime than in one with standard frailty at all ages where $R > 1$. Note that R also influences the magnitude of $CV_{yt}(\delta)$. The slope of the mean mortality rate at age y and time t is:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \frac{\partial \ln(\mu_s(y))}{\partial y} - \bar{\mu}(y,t)(CV_{yt}(\delta))^2 \tag{3.10}$$

Thus, as a result of frailty the slope of the average mortality pattern will differ from the slope of the background mortality pattern and will do all the more so at ages where $R > 1$. By the same token, since $[CV_{yt}(\delta)]$ decreases over time and by age, departures from the slope of background mortality will be smaller at older ages and at more advanced stages of the secular mortality decline.[8]

[7]This expression is also derived by Vaupel and Missov (2014) in the case of constant mortality.

[8]Note that, by construction, $\frac{\partial \ln(\mu_s(y))}{\partial y} = \beta_s(y)$ is invariant over time. The implication of this expression seems to have gone unnoticed in the literature (but see Vaupel and Missov (2014) for an analogous expression and recent discussion). Even in the absence of Barker effects and with an age-invariant $\beta_s(y)$ at adult ages (as in a Gompertz baseline adult mortality pattern), the age-derivative of the average mortality pattern cannot be constant (across ages or across time when there is a mortality decline). The regime of frailty assumed here will always induce an age dependent slope smaller than the standard slope. This has important consequences for the study of old age mortality in that the standard interpretation of an empirical slope estimated after fitting, for example, a Gompertz function to a cohort' s adult mortality rates is probably always incorrect. As suggested by (3.10), such estimate contains an age and time dependent downward bias. To avoid this bias one needs to estimate a Gompertz model controlling *both* for age and for the value of the (age and time varying) negative term in the expression. To our knowledge this has never been done in empirical studies. Elsewhere, we show that Barker effects and mortality decline *will always induce a negative correlation between the levels of child mortality experienced by a cohort and the cohort's adult mortality slope* (Palloni and Beltrán-Sánchez, 2015).

3.2.4 Implications of Barker frailty

We now summarize the most important implications of the expressions derived before. Survivors to age Y_1 can be thought of as a newly 'born' cohort exposed to a mortality regime at ages $y \geq Y_1$ with standard frailty dependent on random frailty equal to $R\delta$ acquired 'at birth', e.g. when reaching the Y_1th birthday, with density $f_{Y_1}(\delta)$, e.g. the conditional density of δ among survivors to age Y_1. At ages older than Y_1 the cohort experiences mortality with standard frailty and extra mortality $R\delta$ and all the algebra of standard frailty applies. Selective survival to age Y_1, as well as mortality decline, operate as factors that reshape the distribution at "birth" (age Y_1) of δ. This interpretation isolates the mechanisms through which Barker effects are manifested. First, to the extent that the secular mortality decline increases the probability of survival to age Y_1, a higher fraction of the initial birth cohort will be exposed to expression of Barker frailty. Second, the force of mortality at ages above Y_1 is shifted upwards directly (through R) and indirectly, via the increased expected values of δ that result from mortality improvements before age Y_1. Third, the conditional survival and expected value of frailty after age Y_1 decreases more rapidly than under standard frailty[9].

As in the case of standard frailty, the slope of average mortality rates at older ages will deviate away from the slope of the standard mortality pattern and will do so more at ages closer to Y_1. From (3.10) one can show that deviations from the slope of background mortality set in and then vanish earlier when the mortality decline is faster. An intriguing aspect of this dynamics is that when R is large, members of birth cohorts who attain ages $y > Y_1$ will be more severely selected out than when R is lower and the selection pressure will be even harsher among those with high values of δ. Standard frailty arguments imply that the opportunity for expressing Barker frailty shrinks rapidly with age since those who are more likely to have a large impact on mortality rates (higher values of δ) will be weeded out sooner after age Y_1. Thus, the resistance that Barker frailty opposes to adult mortality decline will only apply to some ages y in the neighborhood of Y_1 and its durability will be short-lived. A faster mortality decline decreases the windows of time and age within which Barker frailty can visibly slow-down mortality decline. This is an example of negative feedback whereby stronger Barker effects generate mortality conditions that undermine their continued operation and result in more transient and evanescent adult mortality manifestations. The implied non-linear dynamics of this negative feedback remains to be explored. These are surely consequential for empirical investigation since they will define conditions under which the presence of Barker frailty may not be well identified.

3.2.5 Special case I: Gamma distributed Barker frailty

Suppose that $f(\delta)$ is $Gamma(r, \lambda)$ with mean r/λ and variance r/λ^2. The expected value $E_{yt}(\delta)$ is

$$E_{yt}(\delta) = \frac{r}{\lambda + k(t)\Lambda_{sB}(y)}$$

[9] An alternative way of interpreting Barker effects defined above is that they are tantamount to a shift of the standard mortality rates at older ages ($y > Y_1$), e.g from $\mu_s(y)$ to $R\mu_s(y)$.

The time derivative of the expected value $E_y(\delta, t)$ is always positive

$$\frac{\partial \ln(E_{yt}(\delta))}{\partial t} = -\frac{\partial \ln(k(t))}{\partial t} \frac{k(t)\Lambda_{sB}(y)}{\lambda + k(t)\Lambda_{sB}(y)} \tag{3.11}$$

and the age derivative is

$$\frac{\partial \ln(E_{yt}(\delta))}{\partial y} = -\frac{k(t)\mu_s(y)}{\lambda + k(t)\Lambda_{sB}(y)} \tag{3.12}$$

Furthermore, the rate of change over time of average mortality at age y and time t is

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t} \left[1 - k(t)\Lambda_{sB}(y)E_{yt}^{exp}(\delta)\right] \tag{3.13}$$

where $E_{yt}^{exp}(\delta)$ is the conditional expectation of δ under an exponential density, e.g., $r = 1$. The minimum value of expression (3.13) is close to 0, that is, background mortality decline will not be reversed unless the variance of $f(\delta)$ is very large. Note that $\Lambda_{sB}(y)E_{yt}^{exp}(\delta)k(t)$ is the average integrated hazard up to age y in a mortality regime with Barker frailty distributed as $Gamma(1, \lambda)$.

Barker and standard frailty with secular mortality decline generate departures from the standard slope as average mortality will increase more slowly with age. The rate of change of mortality rates is given by:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \beta_s(y) - k(t)\mu_s(y)E_{yt}^{exp}(\delta) \tag{3.14}$$

where $\beta_s(y)$ is the slope of the mortality curve at age y in the baseline mortality pattern.

When frailty is gamma distributed and for ages over Y_1, $E_{yt}^{exp}(\delta)$ is larger under standard frailty and, therefore, the increased attenuation of the mortality slope will be less with Barker frailty than with standard frailty: excess adult mortality brought into the mix by those who express Barker effects will offset the downward bias imparted by standard frailty on the slope of average mortality. In the limit, when y$\rightarrow \infty$ and $E_{yt}^{exp} \rightarrow 0$, the slope of baseline mortality is restored under both standard and Barker frailty. One can show that when $f(\delta)$ is $Gamma(r, \lambda)$ the second age-derivative of the average force of mortality at age y and time t can be positive or negative. This implies that the slope of average mortality rates attains *minima* and *maxima* above age Y_1. But since the slope of the average age pattern of mortality at older ages must converge to the slope of the standard age pattern of mortality, the magnitude of the impact of Barker effects on the slope of average mortality will oscillate, weaken, and then vanish altogether at very old ages.

3.2.6 Special case II: discrete Barker frailty

Suppose there are two groups, one that expresses Barker frailty, (B), with an excess mortality risk at ages over Y_1 equal to λ_B ($\lambda_B > 1$) and the other does not (NB), e.g. $\lambda_{NB} = 1$. Suppose also that the fraction of births who express Barker frailty is a constant g. The average mortality rate at age y and time t is given by

$$\bar{\mu}(y,t) = \mu_s(y)k(t)(P_B(y,t)(\lambda_B - 1) + 1) \tag{3.15}$$

where λ_B is applied to all ages y$\geq Y_1$, and $\mathrm{P}_B(y,t)$ is the fraction of the population who expresses Barker at age y and time t. The expressions for $\mathrm{P}_B(y,t)$ and its derivatives with respect to t are

$$P_B(y,t) = \frac{1}{1 + h\ exp(-k(t)(1-\lambda_B)\phi_s(y))} \tag{3.16}$$

$$\begin{aligned} \frac{\partial P_B(y,t)}{\partial t} &= -\frac{\partial \ln(k(t))}{\partial t}\left[h\ k(t)\phi_s(y)(\lambda_B - 1)P_B(y,t)(1 - P_B(y,t))\right] \\ \frac{\partial \ln(P_B(y,t))}{\partial t} &= \frac{\partial \ln(k(t))}{\partial t}\left[k(t)\phi_s(y)(1-\lambda_B)(1 - P_B(y,t))\right] \end{aligned} \tag{3.17}$$

where $\phi_s(y) = \int_{Y_1}^{y} \mu_s(x)dx$ and $h = (1-g)/g$.

The mean value of frailty at age y and time t is:

$$E_{yt}(\lambda_B) = P_B(y,t)(\lambda_B - 1).$$

Taking logs in (3.15) and then derivatives with respect to time we get

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t} - \left\{\frac{(\lambda_B - 1)(\partial P_B(y,t)/\partial t)}{P_B(\lambda_B - 1) + 1}\right\} \tag{3.18}$$

The term in curly brackets is always positive and expression (3.18) will always be less that the average rate of background mortality decline. Furthermore, the quantity is dependent on changes in $\mathrm{P}_B(y,t)$, and these changes proceed faster at the outset of mortality decline and are gradually spent at advanced stages of the secular decline.

Discrete Barker frailty will also reduce the slope of average adult mortality. The age derivative of the average force of mortality is exactly analogous to (3.18) but with the roles of $k(t)$ and $\mu_s(y)$ interchanged:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \frac{\partial \ln(\mu_s(y))}{\partial y} + \left\{\frac{(\lambda_B - 1)(\partial P_B(y,t)/\partial y)}{P_B(\lambda_B - 1) + 1}\right\} \tag{3.19}$$

Since $(\partial P_B(y,t)/\partial y)$ is always negative, the age-specific slope of average adult mortality will be reduced (relative to the standard) due to Barker effects. The differences will be higher at ages closer to Y_1 and at more advanced stages of the secular decline, when $\mathrm{P}_B(y,t)$ attains a maximum. In the limit, as $t \to \infty$ or $y \to \infty$, the slopes of background and average mortality will be identical.

A model with discrete frailty is appealing since it captures well the idea, implicit in Barker theory, that individuals vulnerable to the impact of adverse early conditions on adult health and mortality are those who experience organ damage *above a given threshold*. The disadvantage of the discrete model is that it requires specification of the threshold, a quantity that is, for all purposes, difficult to either theorize about or empirically estimate.

4 Generalized distributions

An important shortcoming of the continuous and discrete models is that they assume that the allocation of Barker frailty at birth is carried out according to a fixed rule. In fact, in the continuous case the distribution of δ is time-invariant and all births are allocated excess risks (in proportion to δ) by the same probability distribution. In the discrete case the parameter g is the same for all birth cohorts. These are simplifications that fail to translate with high fidelity the nature of Barker frailty defined at the outset.

Two extensions are possible. In the continuous case we can introduce time dependencies in $f(\delta)$ by letting its mean or variance increase hand-in-hand with mortality decline. In the discrete case we can let g be an increasing function of time. Furthermore, one could also include dependencies between the rate of change of the distribution of frailty and/or the rate of mortality decline. These extensions are better suited to capture scenarios where the size and/or heterogeneity of birth cohorts at risk of expressing Barker frailty increases as a result of new epidemiological regimes with better maternal health, fetal, perinatal and early child survival but not triggered by improved nutritional status.

4.1 Gamma Barker frailty with time dependence

The average mortality rate at age y and time t is

$$\bar{\mu}(y,t) = RE_{yt}(\delta(t))\, k(t)\mu_s(y) \tag{4.1}$$

where $E_{yt}(\delta(t))$ refers to the expectation of a random variable $\delta(t)$ that follows a $Gamma(r(t),\lambda)$, $Gamma(r,\lambda(t))$, or $Gamma(r(t),\lambda(t))$.

4.1.1 Time dependence of the "shape" parameter

When the density of random Barker frailty, $f(\delta(t))$, is $Gamma(r(t),\lambda)$ and $r(t)$ is a increasing function of time the dynamic of mortality decline changes by a factor equal to the rate of increase of the mean. In fact,

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} \;=\; \frac{\partial \ln(k(t))}{\partial t}\;\left[1 - k(t)\Lambda_{sB}(y)E_{yt}^{exp}(\delta(t))\right] + \frac{\partial \ln(r(t))}{\partial t} \tag{4.2}$$

The drag force on the background rate of mortality is boosted by the rate of change of *r(t).* Admittedly, $r(t)$ cannot grow indefinitely and should eventually attain a maximum midway through the process. If so, the additional tug exerted by a growing mean frailty will disappear many years after $r(t)$ attains a maximum, when cohorts born under an increasing regime of $r(t)$ complete their passage to ages older than Y_1.

The age specific slope of average mortality at age y and time t is:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \beta_s(y) - \mu_s(y)k(t)E_{yt}^{exp}(\delta(t)) \tag{4.3}$$

Departures from the background or baseline mortality age-specific slopes will be more marked at ages closer to Y_1 (values of $E_{yt}^{exp}(\delta(t))$ for a given t are larger when y remains close to the threshold age Y_1) and among more recent birth cohorts (values of $E_{yt}^{exp}(\delta(t))$ for any age y are larger for higher values of t).

4.1.2 Time dependence of the "rate" parameter of frailty

Assume now that the parameter λ is time dependent so that its value decreases over time (and the variance of $f(\delta)$ increases). The rate of decline of average mortality is:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t}\left[1 - k(t)\Lambda_{sB}(y)E_{yt}^{exp}(\delta(t))\right] - \frac{\partial \lambda(t)}{\partial t}E_{yt}^{exp}(\delta(t)) \quad (4.4)$$

The implication of this expression is that a growing variance of at-birth distribution of frailty leads to rates of decline of adult average mortality that decrease by a larger amount when frailty is fixed: the extra drag force on the rate of decline is directly proportional to the age-time specific mean of frailty in an exponential distribution with rate $1/(\lambda(t) + k(t)\Lambda_{sB}(y))$. Comparing the last two expressions suggests that the additional downward pressure on the rate of mortality decline imposed by changes in the mean of the frailty distribution is age invariant. By contrast the additional downward pressure associated with changes in the variance of the distribution of frailty is age dependent.

The age specific slope of average mortality at age y and time t is:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \beta_s(y) - \mu_s(y)k(t)E_{yt}^{exp}(\delta(t)) \quad (4.5)$$

and departures from the background slope are now dependent on the changing conditional frailty distribution.

4.2 Discrete Barker frailty with changing size of vulnerable population

Suppose there are two groups, one that expresses Barker frailty, (B), with an excess mortality risk λ_B ($\lambda_B > 1$) and the other does not (NB), e.g. $\lambda_{NB} = 1$, and that the fraction of births who express it is $g(t)$, an increasing function of t. The average morality rate at age y and time t is given by (3.15) above but $\mathrm{P}_B(y,t)$ is now a function of the time dependent fraction of individuals who are vulnerable to Barker effects, $(h(t) = (1-g(t))/g(t))$. The expressions for $\mathrm{P}_B(y,t)$ and its derivative with respect to t are

$$P_B(y,t) = \frac{1}{1 + h(t)\ exp(-k(t)(1-\lambda_B)\phi_s(y))} \quad (4.6)$$

and

$$\frac{\partial P_B(y,t)}{\partial t} = -\frac{\partial \ln(k(t))}{\partial t}[h(t)k(t)\phi_s(y)(\lambda_B - 1)P_B(y,t)(1 - P_B(y,t)] - (\lambda_B - 1)\frac{\partial \ln(h(t))}{\partial t} \quad (4.7)$$

Since the rate of change of $h(t)$ is negative, expression (4.7) will be larger than expression (3.17). This shows that the presence of an increasing fraction of births that could express Barker frailty $(g(t))$ acts as an additional brake on the rate of background mortality decline at

older ages. The slope of average adult mortality is identical to expression (3.18) except that $P_B(y,t)$ and its derivative with respect to y are now dependent on $h(t)$: because an increase of the fraction of births who are vulnerable to Barker frailty leads to a positive change in $P_B(y,t)$, there will be a growing tug and deceleration of the rate of adult mortality decline.

5 Simulation of mortality regimes

To provide a sense of the magnitude of Barker effects and some insight into the relations described above, we simulate a series of cohorts undergoing a secular mortality decline using the simple formulation shown in section 3.2.2, that is, $\bar{\mu}(y) = R\,E_{yt}(\delta)\,k(t)\,\mu_s(y)$.

5.1 Simulation steps

We assume the critical age to be 50 ($Y_1 = 50$) after which manifestation of early damage begins to take place in the form of excess mortality risk ($R > 1$) and a Gamma distributed barker frailty (see section 3.2.5). We simulate 50 cohorts starting with a baseline life table with a life expectancy at birth of 40 years at time 0 (from Model Life Tables (Coale and Demeny, 1983)). We then define a yearly mortality decline, $k(t)$, so that the sequence of age-specific mortality rates after 100 years corresponds to a life table with life expectancy at birth of 80 years (i.e., cohort specific life expectancy at birth doubles over a century). The simulation proceeds in three steps as follows:

1. For each of the 50 cohorts we create 300 copies and each of these copies has a random frailty value, $(1+\delta)$, where δ is drawn from a gamma distribution $Gamma(r,\lambda)$ with $r = 1$ and $1/\lambda$ (the standard deviation of the distribution) varying from 1.5 to 4 in .5 increments. That is, we create 8 different variants of frailty regimes and each of these is represented by 300 copies[10].

2. We define six different regimes of Barker effects with excess mortality R ranging from 1.5 to 4 in increments of 0.5. Excess mortality applies to all ages $y \geq Y_1 = 50$. The combination of different gamma distributions for Barker frailty and levels for Barker effects yields 8x6=48 different sets of 50 cohorts each and each of these contains 300 copies.

3. Each of the $i = 1, ..., 300$ copies of cohorts contained in the 48 variants is survived forward with mortality rates $\mu_i(y)$ and survival probabilities $S_i(y)$ that reflect the regime of Barker frailty and Barker effects defined for that copy. At each age $y \leq 100$ we compute the conditional distribution of δ_i, its mean and variance, and the mean mortality rate ($\bar{\mu}(y)$) across all 300 copies of each cohort.

[10]By design, the random terms for frailty,δ, $\delta = \iota + 1$ where $\iota \sim Gamma(1,\lambda)$. Thus, the frailty term we use has a minimum value of 1 and its mean is equal to 1 plus the conditional mean of the gamma random term.

5.2 Illustration 1: secular mortality decline, $R = 1.5$, and time-invariant Gamma frailty with mean and standard deviation 1.5

We first illustrate a scenario with Barker effect of $R = 1.5$ with a time-invariant Gamma frailty distribution with mean and standard deviation 1.5 that applies to all 50 cohorts[11]. We show two sets of results from the simulation, changes over time (Figure 1) and changes over age (Figure 2) of the (log of) average mortality rate, $(\bar{\mu}(y))$, and the (log of) expected value of δ, $(E_{yt}(\delta))$. For simplicity, we show two ages when looking at changes over time (ages 55 and 80) and two cohorts (cohorts 1 or 5 and 50) when examining changes over age. We show average mortality rates in the regime with Barker frailty (solid line), with standard frailty (dashed line), and background mortality in the absence of both Barker and standard frailty (dots).

Figure 1 contains two results. First, panel (a) shows that the average force of mortality at ages 55 and 80 is always higher with Barker frailty. While virtually all the excess mortality at age 55 in a Barker frailty regime is explained by the magnitude of Barker effect ($R = 1.5$), the excess at age 80 is a result of Barker effects as well as of the tightening of selective pressure due to Barker frailty applied to ages over 50. Since these two forces operate in opposite direction, the differences between the average rates at age 80 in a regime with Barker frailty and a regime with standard frailty or background mortality are slightly lower than those at age 55. Furthermore, panel (a) also shows that, as expected from expression (3.13), the decline of the average force of mortality $(\bar{\mu}(x,t))$ is flatter for both ages in either the Barker or standard frailty regimes but more so in the latter than in the former.

The second result in panel (b) is that there are virtually no differences between a standard and Barker frailty regimes regarding the behavior of mean frailty at age 55 because before age 50 both regimes are identical. At age 80, however, Barker frailty has had some room to operate and the levels and trajectories are different: the absolute values of mean frailty are always higher in a standard frailty regime since there are no penalties associated with it past age 50 as there are in a regime with Barker frailty.

Panel (a) of Figure 2 displays effects of frailty regimes on the age slope of adult mortality. As expected from expression (3.14), these panels, corresponding to mortality experiences of the oldest (1) and youngest (50) cohorts, show that the slope of average mortality is flatter in both frailty regimes.

Finally, Panel (b) of the same figure displays the age profile of the average level of frailty in the oldest and youngest cohorts in the standard and Barker frailty regimes. As expected, mean levels of frailty decrease with age but at slightly slower pace when mortality is lower

[11] The simulated scenario is very easy to implement but it has an odd implication. Note that the mortality experience of the birth cohort born 50 years after the onset of secular mortality decline experiences a baseline life table with life expectancy at birth of roughly 60 years. Thus, the period life table corresponding to the year of their birth has a life expectancy at birth lower than 60 years. The sequence of baseline (period) life tables implied by the simulated birth cohorts includes a range of life expectancies at birth from 40 to less than 60 years. This range is only a small fraction of the observed improvements in period life expectancy of low to middle income countries after 1950.

(youngest cohort) and in a regime of standard frailty.

5.3 Illustration 2: secular mortality decline, $R = 1.5$, and time-varying *Gamma* frailty

This case corresponds to the description in section 4.1. We simulate cohorts assuming a fixed Barker effect equivalent to $R = 1.5$ with a *Gamma* distribution with fixed scale parameter, $(r = 1)$, and increasing standard deviation ranging from 1.5 to about 4 over 50 cohorts. As before, we display results showing effects on the rate of average mortality decline and on the expected value of δ (Figure 3), and on the age dependency of mortality rates (Figure 4). In order to highlight the significance of a changing frailty dispersion, these figures also show results from a time-invariant frailty regime with a *Gamma* distribution with scale parameter $r = 1$ and standard deviation 1.5.

Figure 3 displays logs of average mortality (panel (a)) and logs of average frailty (panel (b)) across cohorts at ages 55 and 80 when the parameter λ increases over time (the variance of the gamma distribution increases). Panel (a) shows that a time-varying distribution of Barker frailty exerts a powerful drag on background mortality decline as successive birth cohorts could experience increased mortality rates at ages older than 50. This implies that increased dispersion of the initial distribution of Barker frailty can derail the secular mortality decline. As expected from previous discussion, these changes are non-lineal. Panel (b) of Figure 3 reveals that average frailty increases as background mortality declines and attains a maximum among cohorts in the later stages of the mortality decline. The magnitude of average frailty is higher for younger cohorts, e.g. when Barker effects had time to operate.

Figure 4 panel (a) shows the effects of a growing variance of frailty for the youngest and one of the oldest cohorts (cohorts 50 and 20, respectively) on the slopes of adult mortality. This figure confirms that mortality increases more slowly with age than was the case when the distribution of Barker frailty was time-invariant. Panel (b) of the same figure displays age profiles of the logs of average level of frailty with time-variant and time-invariant Barker frailty regimes. As expected, mean levels of frailty are higher when there is time-variant Barker frailty and they decrease with age everywhere but at slightly faster pace in time-variant Barker frailty regimes.

5.4 Illustration 3: the impact of Y_1 with secular mortality decline, $R = 4.0$, and time-invariant Gamma frailty with mean and standard deviation 1.5

As pointed out at the outset, the basic model developed here contains a massive simplification, namely, we assume that the threshold age Y_1 is constant. Although the assumption is useful because it leads to simpler analytic expressions and to more transparent implications, it can be removed without altering most of the conclusions described before. To illustrate the role of changing Y_1 we resort to a comparison of scenarios with two different values of Y_1. This comparative statics is suggestive and does not replace a more elaborate model where Y_{1i} is a random variable with a systematic and a random individual component for individuals

$i = 1, \ldots, N$ [12].

In these simulations we use two different threshold or ages of onset for Barker effects, early (Y_1=40) and late (Y_1=50) and continue to use the same background mortality, $\mu_s(x)$, secular mortality decline, $k(t)$, and Barker effects R (see section 5 above). However, random frailty values are drawn independently in each of the two scenarios. As a result, when R is small, say $R = 1.5$, there can be only small differences in average mortality rates and average δ at ages close to Y_1 between the two scenarios. This is so because changes in $\bar{\mu}(y,t)$ between the two scenarios are driven by changes in $E_{yt}(\delta)$ (see equation (3.7)) and these differ only marginally between ages 40 and 50. To amplify differences we use a value of $R = 4$ and we obtain illustrations that help visualize better the dynamics of Barker effects. In these simulations we use a time-invariant frailty distribution with mean and standard deviation 1.5 that applies to all 50 cohorts with both early and late Barker onset. As before, we present results showing effects on average mortality, on expected values of δ (Figure 5), and on the age dependency of mortality rates (Figure 6).

Panel (a) of Figure 5 displays the average force of mortality evaluated at two ages (55 and 80) for scenarios with threshold ages 40 and 50. It shows that average mortality rate is always higher when Barker effects start at a later age. The mortality difference between scenarios increases over time with a larger gap at age 55 than at age 80. The result at age 55 is mainly driven by the magnitude of Barker effects ($R = 4$) that elevates overall mortality rates at ages closer to Y_1. As background mortality improves over time, a higher fraction of survivors is exposed to Barker frailty and Barker effects are stronger at age 55 when the onset is at 50 than at 40. At older ages, however, there is an additional force due to the tightening of selective pressure associated with Barker frailty which reduces the difference in mortality rates between the two scenarios.

As shown in panel (b) of the same Figure there are virtually no differences in the behavior of mean frailty at age 80 between early vs. late Barker age at onset. As Barker frailty has had some room to operate up through age 80, it leads to similar frailty values between scenarios. At age 55, however, the levels are different: the absolute values of mean frailty are always higher in late vs. early Barker onset. This is so because there is higher fraction of survivors exposed to Barker frailty at age 55 when the onset is at age 50 than at age 40.

The last figure, Figure 6, permits to assess the effects of changes in threshold ages on the slope of mortality rates at adult ages (Panel a) and on the mean frailty by age (Panel b). The panels, plotting mortality experiences of cohorts 5 and 50, show that the slope of average adult mortality rates is somewhat sharper when the onset of Barker effects occurs earlier in life. Panel (b) of the same figure displays the age profile of the average level of frailty in the same cohorts in the standard and Barker frailty regimes. Mean levels of frailty always decrease with age but at a faster pace when the onset of Barker effects is later. The behavior of the two scenarios converges at older ages.

[12]The idea that Y_1 should be random is consistent with theories of fetal origins according to which there are several chronic illnesses that could play a role and each of them has different time of onset after which Barker effects begin to be felt. Another interpretation is that Barker effects exert an impact on the rate of senescence itself and the slope of the mortality curve begins to accelerate by a random amount after a fixed age Y_1.

6 Concluding Remarks

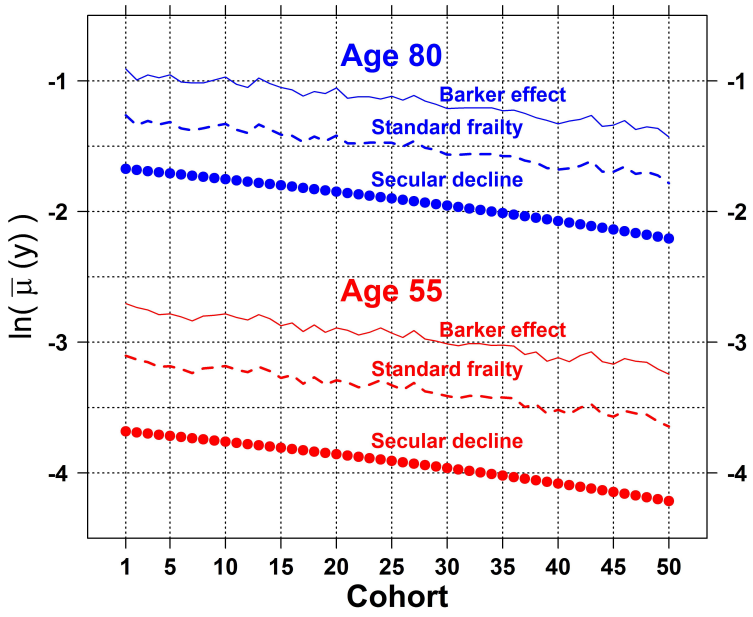
We propose a formal treatment of the demographic consequences of Barker effects on adult mortality rates. We show, mathematically and via simulations, that in a mortality regime with declining mortality, Barker frailty will compound the decelerating force that naturally arises when only standard frailty prevails. This is so because as mortality declines, the selection pressure of standard frailty always weakens over time while Barker frailty imposes an additional force in the form of excess mortality among those who were exposed to adverse early life conditions and attain adult ages. The formulation reconciles standard frailty with Barker frailty as survivors to a certain age (e.g., Y_1) become a cohort that is 'newly born' at age Y_1 that will experience mortality rates with standard frailty and mortality multiplier Rδ (rather than δ as in standard frailty) (Vaupel et al., 1979; Vaupel and Yashin, 1987; Vaupel and Missov, 2014; Aalen, 1988; Steinsaltz and Wachter, 2006). Furthermore, Barker frailty exhibits a distinct dynamic: while standard frailty always leads to deceleration of mortality rates at older ages, Barker frailty unleashes forces that work in the opposite direction and promote increases in the rate of aging at ages above Y_1. When background mortality declines, average adult mortality may go through stages in which mortality will decline more slowly than background mortality rates, remain steady, or even increase. We use standard frailty arguments and suggest, but did not demonstrate, that Barker frailty generates non-linear dynamics in the sense that the manifestation of excess adult mortality implied by Barker frailty undermines its continued operation in a mortality regime [13].

The impact of Barker effects on adult life expectancies is more likely to be observed in countries that experienced mortality declines that were at least partially sustained by massive improvements in infant and child survival. Preliminary findings from Latin American countries, for example, suggest that foregone gains in life expectancy at age 60 associated with Barker effects may be as high as 20% of the projected values over a period of 30 to 50 years (Palloni and Souza, 2013). The changing composition of cohorts by early exposures represents a powerful force that could drag down or halt short-run progress in life expectancy at older ages. The methods developed here facilitate the study of these type of effects with simple, parsimonious models. The task that remains is to translate relations embedded in the model(s) into predicted outcomes and to design empirical tests to falsify such predictions.

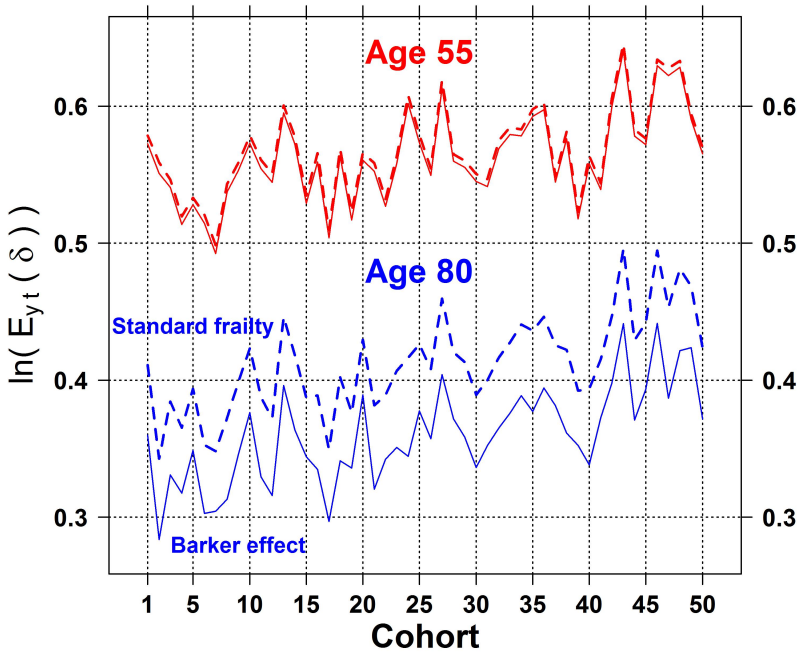
The models described here could be generalized in several directions. Among the most important is to attempt to establish a tight connection between variants of developmental origins theories and the models. Thus, the existence of variable threshold ages and their properties should be deduced from predictions derived from the theories. Similarly, the magnitude of excess mortality associated with Barker frailty should be specified in accordance to the types of chronic illnesses that are known or suspected to be influenced by adverse effects of early conditions. Furthermore, and as suggested by researchers working on senescence (Finch, 2007), adverse early conditions may affect the rate of senescence itself with the implication that our models should impose random effects on the slope of adult mortality, not just on its level. Finally, there is a burgeoning literature (Kuzawa and Eisenberg, 2014)

[13] The study of the precise dynamics of Barker effects necessitates additional investigation.

showing that expression of poor early conditions may implicate germ cells in which case the risk of adult manifestation of early conditions is passed on from one generation to the next. The models proposed here completely ignore this aspect but there is no inherent reason why they could not be extended to incorporate such relations through application of generalized stable population models.

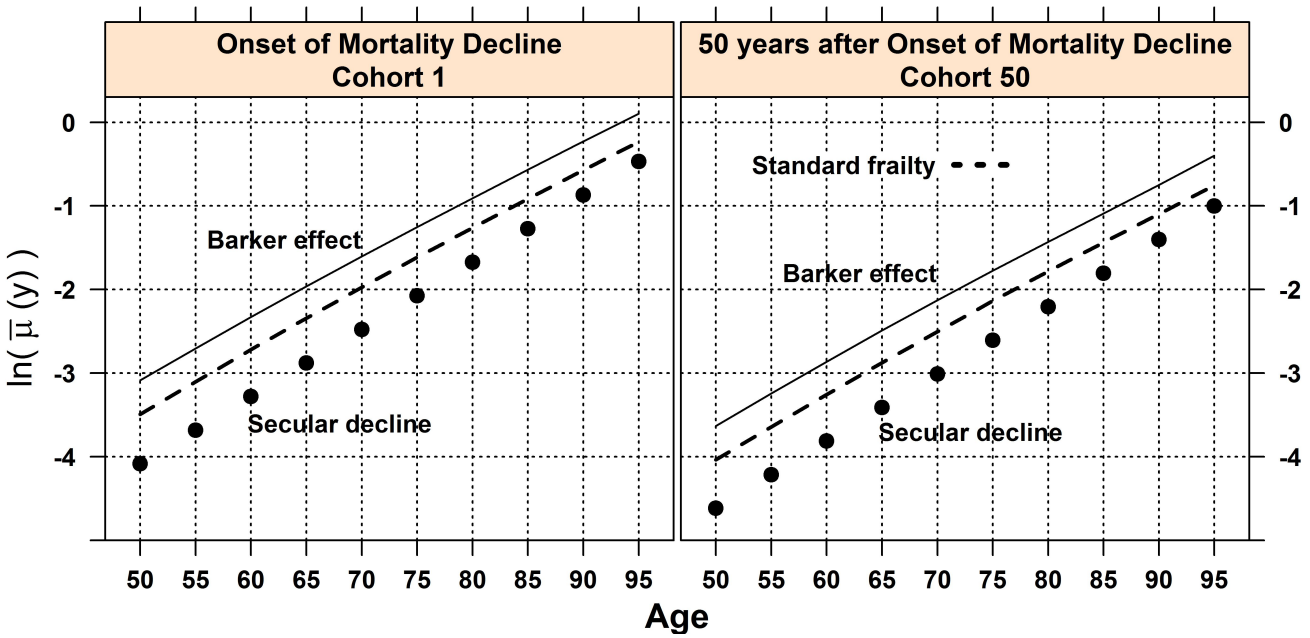


(a)



(b)

Figure 1: Plots of (a) average mortality rates in log-scale, $\ln(\bar{\mu}(y,t))$, and (b) average δ in log-scale, $\ln(E_{yt}(\delta))$, over time for ages 55 and 80 with Barker effect $R = 1.5$ and time-invariant frailty $Gamma(r = 1, 1/\lambda = 1.5)$, respectively.



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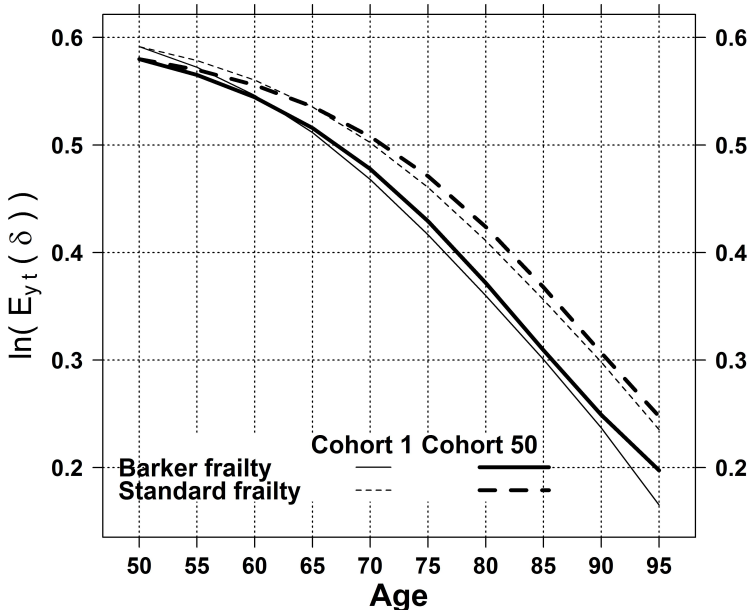
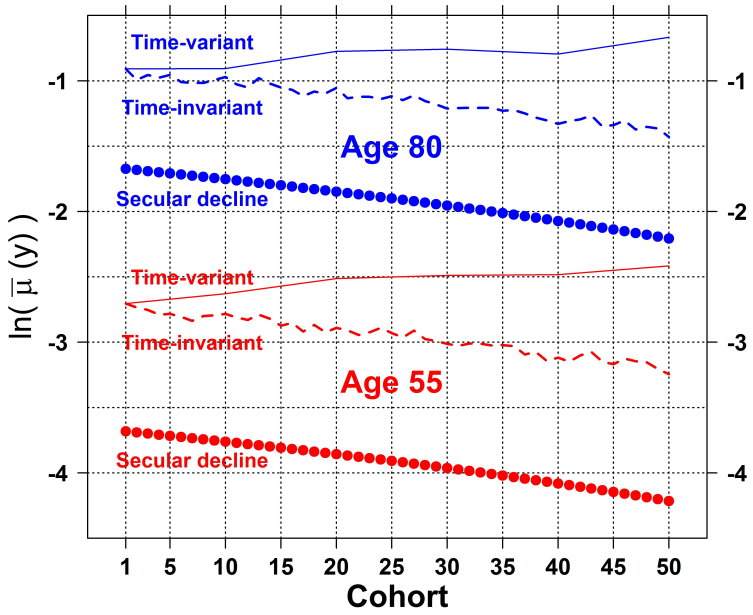


(b)

Figure 2: Plots of (a) average mortality rates in log-scale, $\ln(\bar{\mu}(y,t))$, and (b) average δ in log-scale, $\ln(E_{yt}(\delta))$, by age for cohorts 1 and 50 with Barker effect $R = 1.5$ and time-invariant frailty $Gamma(r = 1, 1/\lambda = 1.5)$, respectively.



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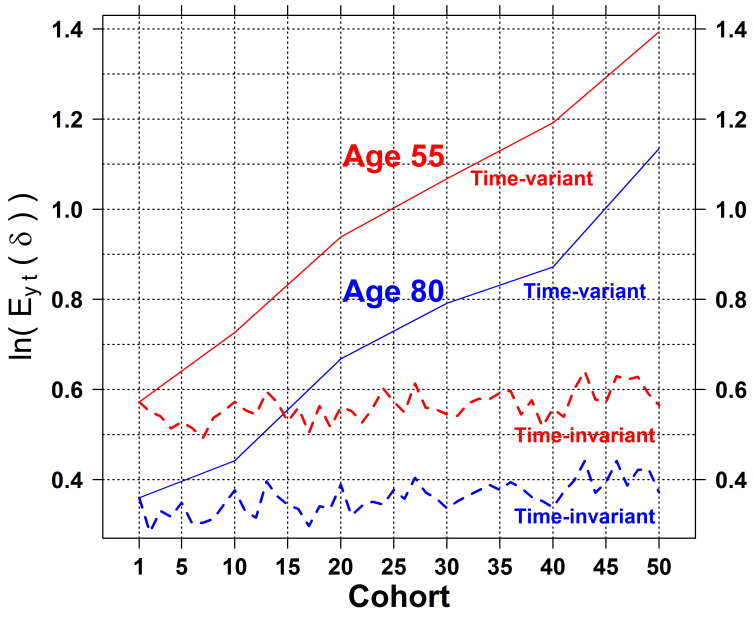
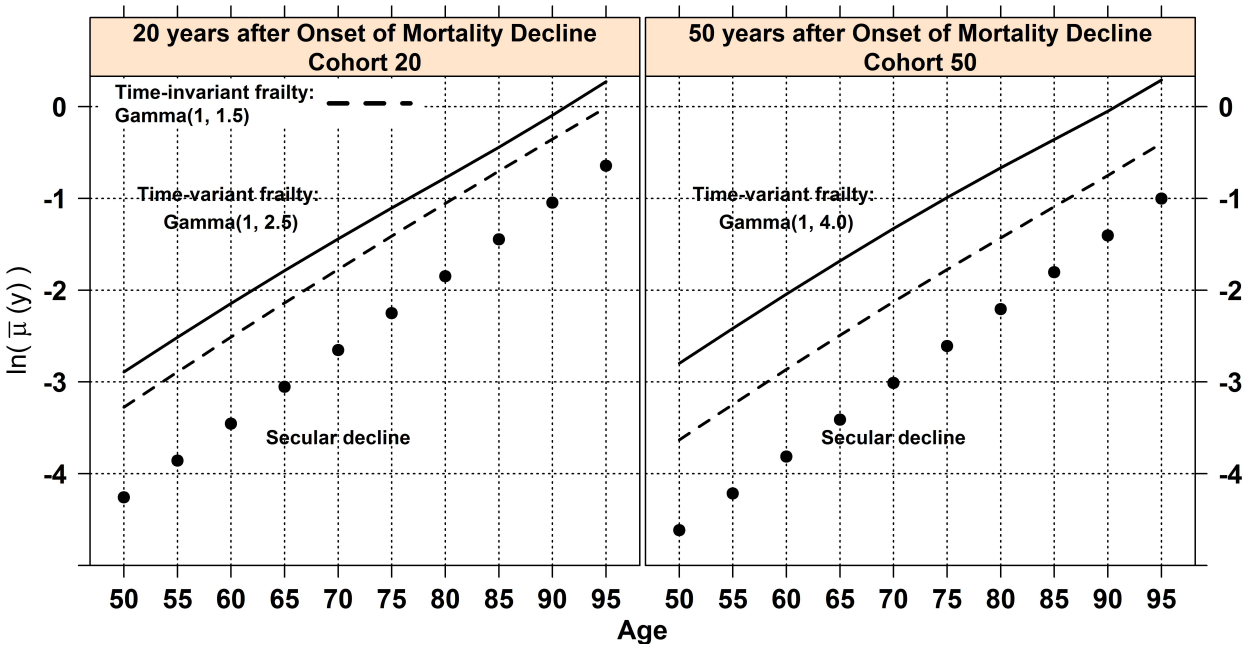
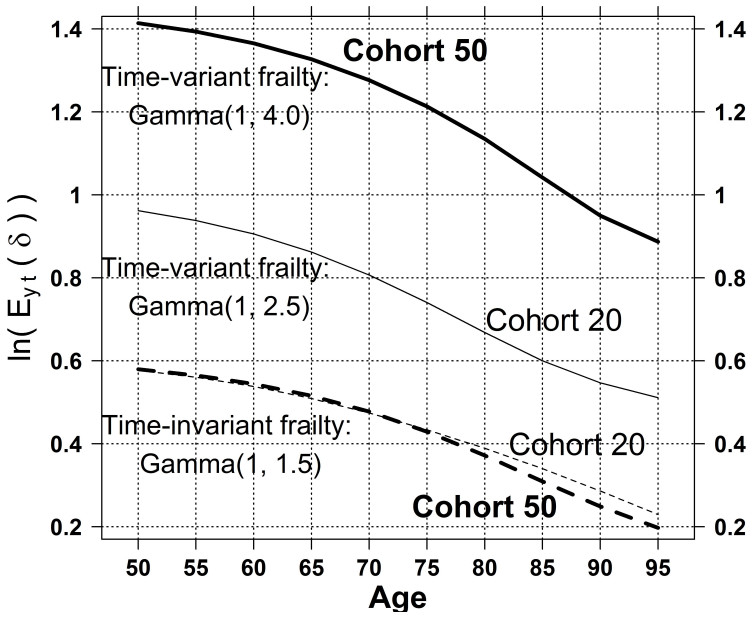


(b)

Figure 3: Plots of (a) average mortality rates in log-scale, $\ln(\bar{\mu}(y,t))$, and (b) average δ in log-scale, $\ln(E_{yt}(\delta))$, over time for ages 55 and 80 with Barker effect $R = 1.5$ and time-variant frailty $Gamma(r = 1, 1.5 \leq 1/\lambda \leq 4.0)$ between cohorts 1 and 50 (see text for further details).

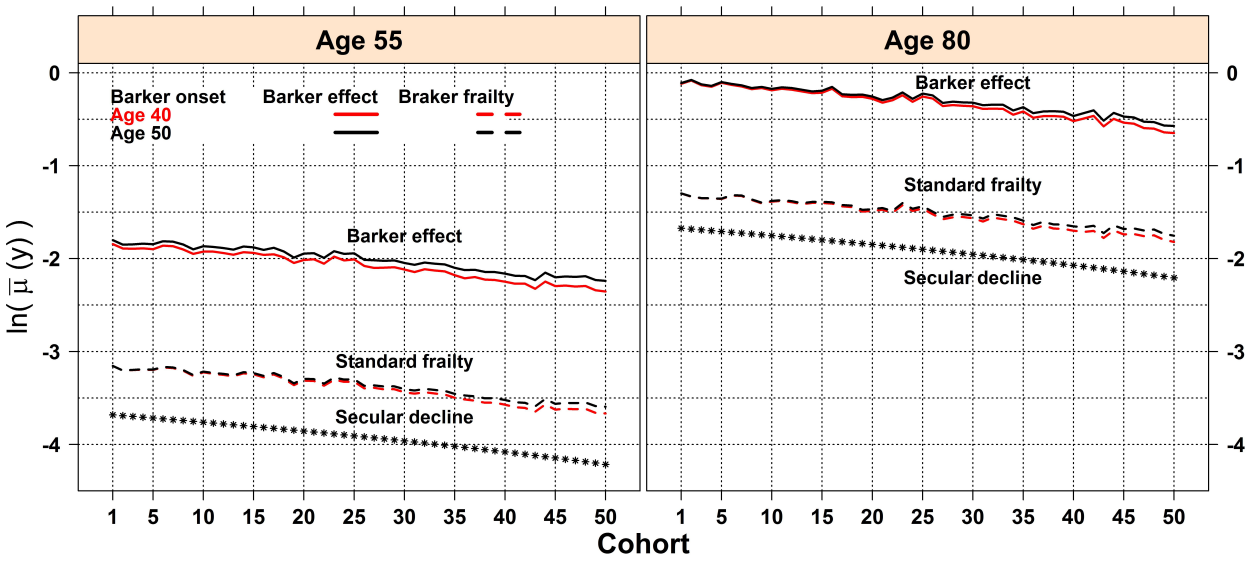


(a)

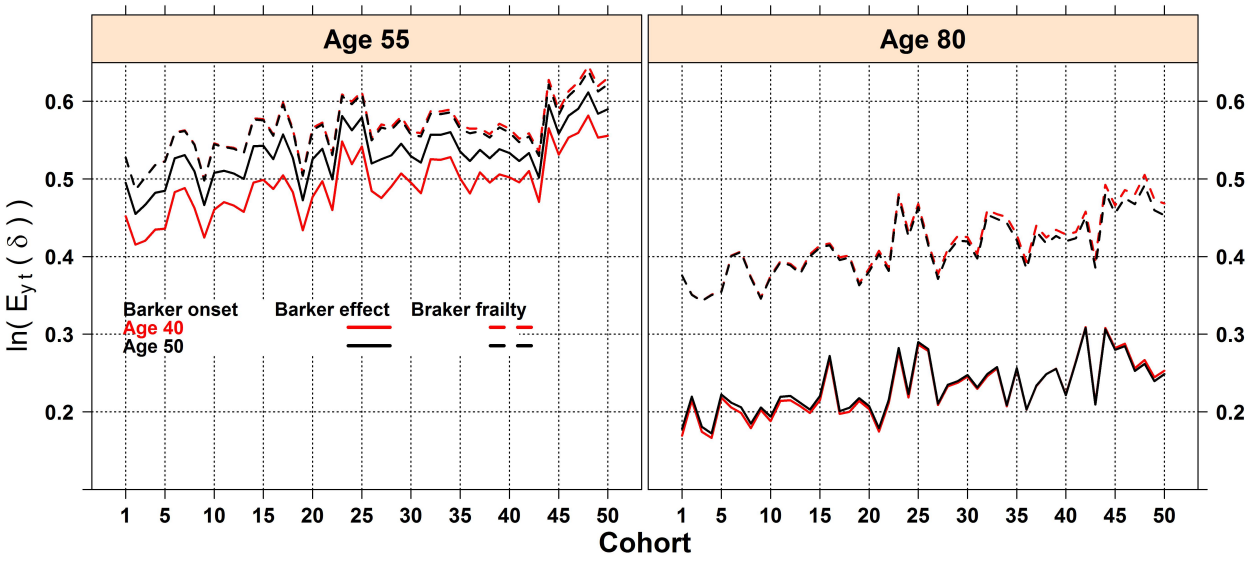


(b)

Figure 4: Plots of (a) average mortality rates in log-scale, $\ln(\bar{\mu}(y,t))$, and (b) average δ in log-scale, $\ln(E_{yt}(\delta))$, by age for selected cohorts with Barker effect $R = 1.5$ and time-variant frailty $Gamma(r = 1, 1.5 \leq 1/\lambda \leq 4.0)$ between cohorts 20 and 50 (see text for further details).

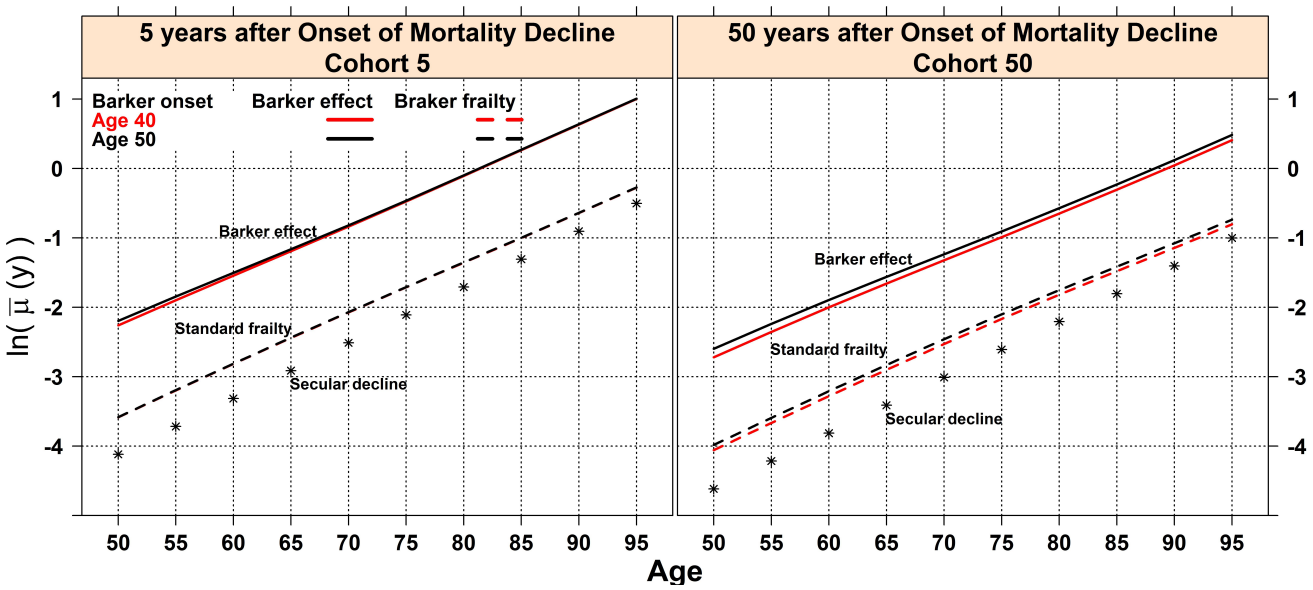


(a)

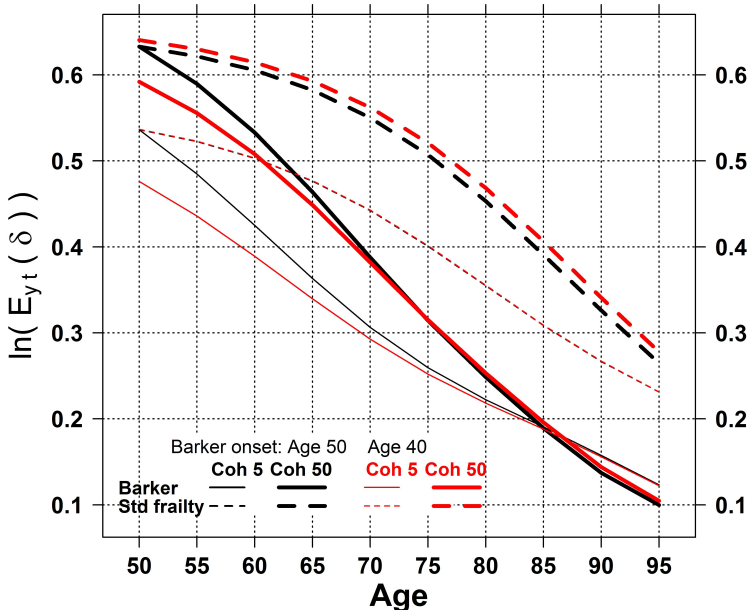


(b)

Figure 5: Plots of (a) average mortality rates in log-scale, $\ln(\bar{\mu}(y,t))$, and (b) average δ in log-scale, $\ln(E_{yt}(\delta))$, over time for early ($\mathrm{Y}_1 = 40$) and late ($\mathrm{Y}_1 = 50$) Barker onset for ages 55 and 80 with Barker effect $R = 4$ and time-invariant frailty $Gamma(r = 1, 1/\lambda = 1.5)$, respectively.



(a)



(b)

Figure 6: Plots of (a) average mortality rates in log-scale, $\ln(\bar{\mu}(y,t))$, and (b) average δ in log-scale, $\ln(E_{yt}(\delta))$, by age for early ($\mathrm{Y}_1 = 40$) and late ($\mathrm{Y}_1 = 50$) Barker onset for cohorts 5 and 50 with Barker effect $R = 4$ and time-invariant frailty $Gamma(r = 1, 1/\lambda = 1.5)$, respectively.

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Appendix. Main definitions

$$
\begin{aligned}
\Lambda_{sB}(y) &= \int_0^{Y_2} \mu_s(x)dx + R\int_{Y_1}^{y} \mu(x)dx \\
\bar{\Lambda}(y,t) &= \Lambda_{sB}(y)k(t)E_{yt}(\delta) \\
E_{yt}^{exp}(\delta) &= \frac{1}{\lambda + k(t)\Lambda_{sB}(y)} \\
E_{yt}^{exp}(\delta(t)) &= \frac{1}{\lambda(t) + k(t)\Lambda_{sB}(y)} \\
\left[CV_{yt}(\delta)\right] Gamma(r,\lambda) &= \frac{\sqrt{r}}{r} \\
\left[CV_{yt}(\delta)\right]^2 Gamma(r,\lambda) &= \frac{1}{r}
\end{aligned}
$$

Appendix Table 1: Summary of formal relations for the rate of change of average mortality rates at age $y >$Y$_1$.

General form $\bar{\mu}(y,t) = RE_{yt}(\delta)k(t)\mu_s(y)$	$Gamma(r,\lambda)$ $\bar{\mu}(y,t) = RE_{yt}(\delta)k(t)\mu_s(y)$	$Gamma(r,\lambda(t))$ $\bar{\mu}(y,t) = RE_{yt}(\delta(t))k(t)\mu_s(y)$	$Gamma(r(t),\lambda)$ $\bar{\mu}(y,t) = RE_{yt}(\delta(t))k(t)\mu_s(y)$
Rate of change with respect to time (t): $\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} =$			
$\frac{\partial \ln(k(t))}{\partial t}\left[1 - \bar{\Lambda}(y,t)(CV_{yt}(\delta))^2\right]$	$\frac{\partial \ln(k(t))}{\partial t}\left[1 - \frac{k(t)\Lambda_{sB}(y)}{\lambda + k(t)\Lambda_{sB}(y)}\right] =$ $\frac{\partial \ln(k(t))}{\partial t}\left[1 - k(t)\Lambda_{sB}(y)E^{exp}_{yt}(\delta)\right]$	$\frac{\partial \ln(k(t))}{\partial t}\left[1 - \frac{k(t)\Lambda_{sB}(y)}{\lambda(t) + k(t)\Lambda_{sB}(y)}\right] - \frac{\partial\lambda(t)/\partial t}{\lambda(t)+k(t)\Lambda_{sB}(y)} =$ $\frac{\partial \ln(k(t))}{\partial t}\left[1 - k(t)\Lambda_{sB}(y)E^{exp}_{yt}(\delta(t))\right] - \frac{\partial\lambda(t)}{\partial t}E^{exp}_{yt}(\delta(t))$	$\frac{\partial \ln(k(t))}{\partial t}\left[1 - \frac{k(t)\Lambda_{sB}(y)}{\lambda(t) + k(t)\Lambda_{sB}(y)}\right] + \frac{\partial \ln(r(t))}{\partial t} =$ $\frac{\partial \ln(k(t))}{\partial t}\left[1 - k(t)\Lambda_{sB}(y)E^{exp}_{yt}(\delta(t))\right] + \frac{\partial \ln(r(t))}{\partial t}$
Rate of change with respect to age (y): $\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} =$			
$\frac{\ln(\mu_s(y))}{\partial y} - \bar{\mu}(y,t)(CV_{yt}(\delta))^2 =$ $\beta_s(y) - \bar{\mu}(y,t)(CV_{yt}(\delta))^2$	$\beta_s(y) - \frac{\mu_s(y)k(t)}{\lambda + k(t)\Lambda_{sB}(y)} =$ $\beta_s(y) - \mu_s(y)k(t)E^{exp}_{yt}(\delta)$	$\beta_s(y) - \frac{\mu_s(y)k(t)}{\lambda(t) + k(t)\Lambda_{sB}(y)} =$ $\beta_s(y) - \mu_s(y)k(t)E^{exp}_{yt}(\delta(t))$	$\beta_s(y) - \frac{\mu_s(y)k(t)}{\lambda + k(t)\Lambda_{sB}(y)} =$ $\beta_s(y) - \mu_s(y)k(t)E^{exp}_{yt}(\delta(t))$