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Authors
Palloni, Alberto
Beltrán-Sánchez, Hiram

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Discrete Barker frailty and warped older age mortality dynamics*

Alberto Palloni† Hiram Beltrán-Sánchez‡

Abstract

We develop a discrete variant of a general model for adult mortality influenced by the delayed impact of early conditions on adult health and mortality. The discrete variant of the model builds on an intuitively appealing interpretation of conditions that induce delayed effects and is an extension of the discrete form of the standard frailty model with distinct implications. We show that introducing delayed effects is equivalent to perturbing adult mortality patterns with a particular class of time(age)-varying frailty. We emphasize two main results. First, populations with delayed effects could experience unchanging or increasing adult mortality even when background mortality has been declining for long periods of time. Although this phenomenon also occurs in a regime with standard frailty, the distortions can be more severe under a regime with Barker frailty. As a consequence, conventional interpretations of the observed rates of adult mortality decline in societies that experience Barker frailty may be inappropriate. Second, the observed rate of senescence (slope of adult mortality rates) in populations with delayed effects could increase, decrease or remain steady over time and across adult ages even though the rate of senescence of the background age pattern of mortality is time and age invariant. This implies that standard interpretations of empirical estimates of the slope of adult mortality rates in populations with delayed effects may be misleading since they can reflect mechanisms other than those inducing senescence as conventionally understood in the literature.

Key Words: Barker hypothesis, Early origins of health and disease, Old age mortality, Demographic frailty

1 Introduction

We derive a discrete model to represent delayed adult mortality effects of unfavorable early life conditions. The model is built on an intuitively appealing interpretation of conditions that induce delayed effects, removes assumptions that limit the applicability of a continuous version (Palloni and Beltrán-Sánchez 2015a), and formalizes the implications for observed mortality patterns of

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†Center for Demography of Health & Aging, University of Wisconsin-Madison. Email: palloni@ssc.wisc.edu.

‡Department of Community Health Sciences at the Fielding School of Public Health & California Center for Population Research, both at UCLA. Email: beltrans@ucla.edu

several mechanisms producing delayed effects on adult health and mortality. The paper rests on two simplifications. First, although there are multiple pathways through which early life conditions can manifest themselves as delayed effects, the current model treats all of them as if they share the same dominant features and ignores dissimilarities. The simplification is needed to make the model tractable as a simple generalization of the standard frailty model (Vaupel et al. 1979; Vaupel and Yashin 1987; Vaupel and Missov 2014). Second, unlike the continuous version of the model, it assumes that early conditions can be treated as a 1/0 binary variable and the population at birth classified into those who did and those who did not had adverse experiences.

The plan of the paper is as follows: in section 2 we define the concepts of Barker frailty and Barker effects. Section 3 describes variants of the discrete model for Barker frailty that are suitable to describe different Barker frailty regimes. In Section 4 we describe simulations to assess the impact of Barker frailty on adult mortality rates and review selected results. The last section discusses implications of the model for demographic interpretation of human mortality patterns and proposes extensions of the model.

2 Barker frailty[1]

2.1 Mechanisms

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

[1] A word about the choice of these labels is necessary. We use the term "Barker frailty" to refer to a trait that reflects adverse early life experiences and Barker effects to the impact of Barker frailty on adult mortality rates. These labels are simplified shorthand to refer to a wide range of mechanisms, including, but not reduced to, those suggested by Barker, as if all of them shared the same properties.This is a simplification that improves tractability but that should be improved upon.

influence on adult health and mortality (Barker 1998; Gluckman and Hanson 2006; McDade and Kuzawa 2004; Langley-Evans 2004; Beltrán-Sánchez et al. 2012; Barouki et al. 2012; Gluckman and Hanson 2006; Bateson and Gluckman 2011). The mechanisms that trigger these delayed effects involve perturbation of cell attrition, growth and functional differentiation, various classes of epigenetic changes (histone covalent modifications, non-coding RNA expression, methylation) allowing the expression of developmental plasticity, and, more generally, conditions including exposure to acute poverty, deprivation, and stress (Forsdahl 1977, 1978). The best known, albeit not the most general, version of the hypothesis of delayed health effects, was articulated by Barker (Barker 1998). The cornerstone idea of this version of the theory ('fetal programming') is that nutritional deprivation *in utero*, and soon after birth, disrupts processes of organ formation (cell division, growth and functional specialization) and exposes survivors to excess risk of 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.

A more recent formulation is associated with processes of predictive adaptive response (PAR), and more generally with theories of Developmental Origins of Adult Health and Diseases (DOHaD), operating either as homeostatic adaptation or epigenetic adjustment to experienced or predicted environmental challenges (Bateson and Gluckman 2011; Gluckman and Hanson 2006). Recent empirical research identifies the possibility that exposure *in utero* and perinatal experiences may lead to epigenetic changes that could result in permanent immune or metabolic dysfunctions later in life. The most intriguing of these are alterations of the microbiome during delivery and right after birth (Bateson and Gluckman 2011). Indeed, there is growing empirical evidence showing a link between type of delivery, composition of the newborn's gut bacterial population, and risks of

adult T2D (Devaraj et al. 2013; Giongo et al. 2011).

An older, related, but better established strand of the literature identifies linkages between exposure and contraction of 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 contraction of well-defined infections induces organ damage that manifests itself as adult chronic illnesses among survivors (Fong 2000; Elo and Preston 1992).

A third mechanism linking early conditions and adult health via delayed response involves sustained inflammation that results from recurrent episodes of infectious diseases during early childhood, persistent 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 not episodic but long lasting, they are likely to increase susceptibility to a number of adult chronic illnesses (Finch 2007).

These mechanisms share one important feature and differ in one important respect. The commonality is the presence of deviant organ differentiation and development or damage and/or abnormal immune/metabolic responses with long latency periods and delayed manifestations in late adulthood. The difference between mechanisms is the role played by environments and experiences throughout life. Thus, whereas fetal programming and developmental plasticity working through epigenetic modifications require mismatches between pre and perinatal environment and postnatal experiences, the mechanisms working through infections or sustained inflammation require vulnerability to infectious diseases, perhaps established at birth, and exposure to and/or contraction of those diseases later in life. The discrete model introduced below enables us to capture both the

presence of adverse pre and perinatal environments and susceptibility to disease using a single trait (defined at birth) with age varying effects on mortality.

2.2 Conditions of observability

Delayed expression of damage inflicted by early experiences will be observable in adult mortality patterns only if the following three 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 relatively high fatality rates; (c) the beneficial mortality-related effects of medical technological advances adopted and diffused between the time of onset of early 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 the offending chronic conditions. Below we show formally that in populations where all three conditions are satisfied adult mortality will exhibit two singularities, one affecting time trends and the other distorting age patterns.[2]

3 Models for discrete Barker frailty[3]

The model for Barker frailty includes three properties. First, individuals are characterized by a propensity, $0 \leq \delta < \infty$ (Barker frailty), acquired before or at birth and carried through life that makes them more or less likely to produce delayed health and mortality effects (Barker effect). In the discrete version of the model a delayed manifestation only occurs if the trait's value exceeds

[2]Evidence from animal studies has confirmed several tenets of DOHaD and Barker theories (Bateson and Gluckman, 2011) but empirical evidence from human populations is less favorable, inconsistent, and generally identify effects of small magnitudes (Bengtsson and Lindström 2000; Roseboom et al. 2001; Painter et al. 2005; Madsen et al. 2010; Lundborg 2008). However, there is scarce if any evidence drawn from countries that experience the types of mortality decline and environmental and ecological conditions that we highlight here as conditions for observability of Barker effects.

[3]What follows is particular case of a more general model for Barker frailty. See Appendix.

a threshold (Barker threshold).[4] The actual expression of effects in the form of excess mortality and ill-health throughout the life course could depend on individual experiences following birth. In particular, the magnitude of delayed adult effects should be a function of accumulated exposures that trigger or inhibit the expression of frailty. The model with discrete frailty is appealing since it captures well the idea, implicit in Barker fetal programming theory, that individuals vulnerable to the impact of adverse early conditions on adult health and mortality are those who experience deprivations *above a given threshold*. The disadvantage of a discrete model is that it requires direct or indirect specification of the threshold, a quantity that is, for all purposes, difficult to either theorize about or empirically estimate.

Second, since it is the mortality implications of the frailty trait that matter, one can pose that δ has a changing impact on mortality as a result of exposures throughout various stages of the life course. In the more general form of the model the trait can potentially have three different effects on the force of mortality: before an early age Y_0, after a critical adult age Y_1, and in the age interval (Y_0, Y_1). In this paper we only include delayed effects past age Y_1 (see Appendix for a more general formulation).

Third, the fraction of individuals at adult ages who could express Barker frailty must increase whenever mortality declines. This can take place via three different mechanisms. The first operates by simply reducing selective pressure: individuals who would have died early in life in a higher

[4]The difference between standard and Barker frailty traits is that the former is fixed at birth whereas, at least conceptually, the latter could be shaped by early postnatal experiences. None of the mechanisms we described at the outset can be entirely captured by a trait fixed at birth. Thus, the distribution at birth of δ must reflect both the at birth-distribution and prospective changes that result from subsequent heterogeneous individual experiences. It is thus a trait with a more complex genesis that cannot be well-specified unless we know the impact of post-birth experiences on the at-birth trait or propensity. To circumvent this conceptual problem, one can think of the distribution of δ at birth as what would be observed at a very early age beyond which additional experiences do not affect the underlying quantity *in the absence of mortality up to that age*. In this case the distribution of δ as the outcome of the mixing of the distribution of fixed-at-birth susceptibility and the (unconditional on survival) probability of subsequent exposures that promote delayed manifestations. Thus, δ acts as a *net propensity*, induced by *in utero* deprivation or subsequent exposures to express delayed manifestations.

mortality regime can survive to adult ages in a more beneficial mortality regime and some of them will be carriers of higher values 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 it, irrespective of mortality changes. This is possible 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 changes can be captured by redefining the density of δ. A third mechanism induces a downward shift of Barker threshold (in the absence of changes in the initial density of δ) and could capture situations involving changes in epidemiological regimes or environmental conditions that place children at higher risk.

3.1 Model with fixed critical ages and mortality decline

We assume that (a) the fraction of births at time t that can express Barker frailty is a fixed quantity, $P_B(0,t) = g$ and (b) that Barker effects are equivalent to a relative mortality risk equal to λ_B ($\lambda_B > 1$) applicable only at adult ages $y > Y_1$.[5] We also assume that the fraction of births in the cohort that does not carry Barker frailty, $(1-g)$ do not express Barker frailty so their excess mortality risk at ages over Y_1 equal to $\lambda_{NB} = 1$. The first simplification is tantamount to fixing *ex ante* the complement of the distribution function for the random trait δ to be $\psi(\delta)$, and to assume δ_0 such that $\psi(\delta_0) = g = P_B(0,t)$. The second simplification is equivalent to assuming that relative risks associated with Barker frailty are age invariant at ages older than Y_1 and set to $R(\delta, y) = \lambda_B$ for $y > Y_1$ and $R(\delta, y) = 1$ everywhere else.

Assume that the mortality regime undergoes a secular change with onset at $t = 0$ and that

[5]The assumption that Barker frailty leads to mortality excess only at adult ages downplays the consequence of Barker frailty *in a secular mortality decline*. This is because the proportional gains in survival to older ages implied by an arbitrary rate of background mortality decline should be higher when there is no excess mortality at younger ages. As a consequence our model understates the effects of Barker frailty.

each birth cohort is exposed to a mortality level corresponding to the year when they were born. Thus, members of a birth cohort born $t > 0$ 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 baseline mortality pattern characterized by mortality rates $\{\mu_s(y)\}$ and that the force of mortality for year t ('background' mortality) is $\mu(y,t) = k(t) \times \mu_s(y)$, where $k(t)$ is a monotonically decreasing function of time (linear or exponential).[6] Thus, the force of mortality at age $y \geq Y_1$ for a member of a cohort born in year t is given by

$$\bar{\mu}(y,t) = \mu_s(y)k(t)(P_B(y,t)(\lambda_B - 1) + 1). \tag{3.1}$$

The expected value of *excess mortality* at age y and time t is:

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

and the attributable mortality associated with Barker frailty is given by

$$AM_{yt}(\lambda_B) = \frac{P_B(y,t)(\lambda_B - 1)}{1 + P_B(y,t)(\lambda_B - 1)}$$

where $P_B(y,t)$ is the fraction of the population who expresses Barker at age y and time t.[7] Taking logs in (3.1) and then derivatives with respect to time we get an expression for the rate of change over time of the aggregate mortality rates

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t} + AM_{yt}(\lambda_B)\frac{\partial \ln(P_B(y,t))}{\partial t}. \tag{3.2}$$

The term after the addition sign is always positive and expression (3.2) will be less (in absolute value) than the average rate of background mortality decline. Furthermore, the quantity is dependent on changes in $P_B(y,t)$ that proceed faster in the initial stages of the mortality decline

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

[7] The expressions for $P_B(y,t)$ and its derivatives with respect to time t and age y are shown in the Appendix.

and are gradually spent later on in the process. This expression illustrates the first singularity due to Barker frailty, namely, a distortion of the rate of mortality decline.

Discrete Barker frailty also flattens the slope of average adult mortality. In fact, the age derivative of the average force of mortality is exactly analogous to (3.2) but with the roles of $k(t)$ and $\mu_s(y)$ interchanged:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \frac{\partial \ln(\mu_s(y))}{\partial y} + AM_{yt}(\lambda_B)\frac{\partial \ln(P_B(y,t))}{\partial y}. \tag{3.3}$$

Since $\partial P_B(y,t)/\partial y$ is always negative, the age-specific slope of average adult mortality will be smaller than the slope in the background mortality pattern due to Barker effects.[8] The differences will be higher at ages closer to Y_1 and at more advanced stages of the secular decline when $P_B(y,t)$ attains its maximum. In the limit, as $t \to \infty$ or $y \to \infty$, the slopes of background and average mortality will be identical. This expression illustrates the second singularity (affecting the age pattern of adult mortality) described above.

Because theories of secular mortality decline assign importance to time trends of the rate of change of mortality and theories of senescence focus on variation of the adult mortality slope and correlations with early mortality, it is important to describe two additional features: (a) the age-specific time trajectory of the reduction in the rate of mortality decline relative to the background rate of mortality decline; and (b) the time and age specific changes of the rate of increase in adult

[8] By construction, $\frac{\partial \ln(\mu_s(y))}{\partial y} = \beta_s$ is age and time invariant. The implication of this expression seems to have gone unnoticed in the literature (but see Vaupel and Missov (2014) for an analogous expression for continuous frailty). 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 the expression, such estimate contains an age and time dependent downward bias. To avoid this bias one needs to estimate a Gompertz model controlling for *both* age and 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 2015a,b).

mortality rates relative to the adult mortality slope in the background mortality pattern. The pertinent indicators are defined in Palloni and Beltrán-Sánchez (2015b), their graphic profiles are displayed in the appendix and their implications are discussed in the section below.

3.2 Model with random critical ages and mortality decline

The simple model above contains a massive simplification, namely that the critical age is fixed. However, most DOHaD theories imply, explicitly or not, that critical ages are themselves a function of individual experiences, individual traits, and features of the background epidemiological regime. That is, critical ages must have both a systematic and a random component. Because our knowledge about the operation of the three mechanisms for Barker effects is not robust enough, it is difficult to include in the model the factors that determine these critical ages. And, even if we did, it would be a daunting task to identify and properly specify the components of these ages as they are likely related to accumulation of adverse experiences throughout the life course.

Without precise knowledge of determinants of critical ages we can only assess the influence that random critical ages have on the magnitude and patterns of effects of Barker frailty on adult mortality. This is important since by doing so we will at least be able to approximately gauge the role these ages play in the overall impact of Barker frailty and effects on adult mortality patterns and trends.

We extend the model so that critical ages are now randomly determined (but devoid of a systematic component). For clarity and compactness of notation we relabel the critical age as Z and assume it has a well-defined density $f_Z(z)$ for all individuals who belong to the subgroup endowed with Barker frailty. A critical age is irrelevant for all those who cannot express Barker frailty. Further, assume that $Z \geq 40$ so that Barker effects are nil below age 40. Elsewhere (Palloni and Beltrán-Sánchez 2015b) we show that the expected value of the force of mortality at some age

$y \geq 40$ can be approximated by the following expression:

$$\bar{\mu}(y,t) \simeq k(t)\mu_s(y)[P_B^1(y,t)\Phi_Z(y)(\lambda_B - 1) + 1] \tag{3.4}$$

where $\Phi_Z(y)$ is the distribution function of critical ages z evaluated at age y and $P_B^1(y,t)$ is the fraction of all survivors to age y who carry Barker frailty *and* whose critical ages satisfy $z \leq y$.[9] Expression (3.4) makes it plain that the introduction of random critical ages erodes the impact of Barker frailty as it is now associated with a smaller subset of individuals who survive to age y, $P_B^1(y,t)$: not all of those who could express Barker frailty but only those whose critical ages are younger than age y . However, as $y \to \infty$, the fraction of the cohort with Barker frailty that does not influence mortality level (because their critical ages are higher than y) diminishes rapidly. As a consequence, the dilution of the mortality impact of Barker effects decreases and converges to what would have been observed had the critical age been fixed at age 40. The main result is that the rates of change of mortality rates and adult mortality slopes are now:

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial t} = \frac{\partial \ln(k(t))}{\partial t} + AM_{yt}^1(\lambda_B)\frac{\partial \ln(P_B^1(y,t))}{\partial t}$$

and

$$\frac{\partial \ln(\bar{\mu}(y,t))}{\partial y} = \frac{\partial \ln(\mu_s(y))}{\partial y} + AM_{yt}^1(\lambda_B)\frac{\partial \ln(P_B^1(y,t))}{\partial y}.$$

These are expressions analogous to (3.2) and (3.3). The difference between these and the previous expressions is that the driver of the rates of change is $AM_{yt}^1(\lambda_B)$, a quantity that is always strictly smaller than $AM_{yt}(\lambda_B)$. As a consequence, the effects of Barker frailty on the baseline rate of mortality decline and on the adult slope will be lower than if critical ages are fixed and equal to the lowest bound (e.g., at age 40).

[9] An expression for $P_B^1(y,t)$ is in the Appendix.

In summary, when critical ages are random the influence exerted by Barker frailty on both the rate of mortality decline and on the adult mortality slope is reduced. The magnitude of this reduction depends on the nature of the cumulative distribution function of Z: to the extent that the probability mass for Z is located at older ages, the impact of Barker frailty will be minor. The effects will be stronger and converge to those associated with a regime with fixed critical ages when the probability mass is located at younger adult ages.

3.3 Model with fixed critical ages, changing size of vulnerable population and mortality decline

An important shortcoming of the models above is that it assumes the relative size of the population who could express Barker frailty is fixed across birth cohorts. This simplification fails to translate with high fidelity the nature of Barker frailty defined before. The most natural extension is to let $P_B(0,t) = g(t)$ be an increasing function of time. This can be the result of a change in the distribution of the latent Barker frailty trait δ or of a downward shift of Barker threshold. In either case the extension is 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, lower fetal and perinatal mortality, and/or worse interaction effects of early environments and Barker frailty.

Suppose the fraction of births who express Barker frailty is $g(t)$, an increasing function of t. The average mortality rate at age y and time t is given by (3.1) but $P_B(y,t)$ 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 $P_B(y,t)$ is

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

This is identical to the expression defined before with $h(t)$ replacing h. The derivatives of $\bar{\mu}(y,t)$ with respect to t and y are analogous to those for the case of time invariant h with one significant difference, namely, $P_B(y,t)$ and $AM^1_{yt}(\lambda_B)$ are now influenced by the decreasing time-varying odds, $h(t)$ of being born free of Barker frailty. Because $h(t)$ decreases over time, both the rate of change of average mortality and the slope of adult mortality will deviate more from the baseline parameters than in the case when h is fixed. Analogous expressions to those above hold for the case when critical ages are random. In all cases one must replace $P_B(y,t)$ and its derivatives for $P^1_B(y,t)$ and its derivatives.

4 Simulation of mortality regimes

To evaluate the magnitude of Barker effects and to gain insights on the relations described above, we simulate a series of cohorts undergoing a secular mortality decline and expose them to several variants of discrete Barker frailty, with fixed and random critical ages. The objective of the simulations is to shed light on the behavior of two functions, the age-specific rates of mortality change and the adult mortality slope across birth cohorts. The details of the simulation are in the Appendix.

4.1 Results

The most important results of the simulation with fixed critical age (at 40) are displayed in Figures 1 to 4. Because in the case of random critical ages the *patterns* of results are identical to those in the case of fixed critical ages, albeit with effects of smaller magnitude, we omit the corresponding figures. Figure 1 displays estimated slopes of adult mortality by birth cohort separately for populations with different levels of prevalence of Barker frailty (4 panels, one for each population) and by lowest bound of age considered in the estimation of the adult mortality slope (40, 50, 60 and 70). In addition, each figure distinguishes three different cases according to levels of Barker effects: 1.5

(blue), 4 (red), no excess or baseline (gray). The first feature observed in the figure is that, as expected, in all cases the adult mortality slope declines with birth cohort. The magnitude of the difference between a cohort's slope and the baseline slope varies but can attain values as high as 0.020 for 23% error. Considering that the width of the range of plausible human adult mortality slopes is not larger than 0.04-0.08, the magnitude of the absolute error is substantial. The second feature is that deviations of each cohort's slopes from the baseline increases for more recent cohorts. If the simulation had involved a larger number of cohorts, the deviations would have attained a maximum and then began to recede until becoming negligible. The third feature is that Barker excess matters a great deal. Indeed, the scenario with excess mortality equal to 1.5 generates a trajectory very close to the one that obtains if only standard frailty applies and produces much gentler deviations than the scenario with heavier adult mortality penalties. The final feature of Figure 1 is that the population with a larger fraction of births susceptible to Barker effects presents the largest deviations of adult slopes from baseline adult slope.

[Figure 1 about here]

Figure 2 displays the average rate of mortality decline by adult age separately by levels of prevalence of Barker frailty. In each graph we jointly plot the rates of decline estimated for the baseline scenario (gray), and two scenarios differing in the magnitude of excess mortality, 1.5 (blue) and 4 (red). By design, the absolute magnitude of the decline increases with age but the concavity of the curves differs substantially across scenarios: when excess adult mortality is high, the rates are well below the baseline for all ages above 55-60 (and before age 90-95) and of lower absolute magnitude at ages below 55-60 though the differences here are trivial. The average relative difference between the most severe Barker regime and the baseline is as high as 50% at age 72.5 when Barker effects are set to 4.

[Figure 2 about here]

Figures 3 and 4 illustrate patterns of relations between a cohort's early mortality and measures of adult mortality, and Tables 1 and 2 show correlation coefficients associated with these patterns. In each figure, open circles represent older cohorts (i.e., those born in the early stages of the mortality decline) and closed circles correspond to recent cohorts. Figure 3 plots the relation between the estimated Gompertz slope of a cohort and the level of infant mortality experienced by the same cohort. The figure includes four cases corresponding to different levels of prevalence of Barker frailty and four cases for different lower bounds of ages included in the estimation of a cohort's slope. The key feature is that in all cases the presence of Barker frailty induces a positive correlation where there is none (Table 1). The correlation is strongest when Barker effects are larger and when the range of ages included in the estimation of the slope are older. Researchers conventionally use age 50 or 60 as a lower bound but even in these cases the slope induced by Barker frailty is substantial and the larger the magnitude of Barker effects, the steeper the slope becomes. Figure 4 plots a cohort's mortality rates in three different adult age groups and its correspondent infant mortality. The key feature is NOT the disparities of the curves' levels, as these depend on mortality levels associated with the cohorts, but rather the slope of the curves:[10] in all cases these are flatter than the baseline and the larger the magnitude of Barker effects, the flatter they get (Table 2). Figures 3 and 4 confirm the main implication of the main model: when declining mortality are driven by Barker frailty any correlation between observed cohort's early and adult mortality will be deceiving as it will suggest patterns that are absent, the result of artifacts produced by Barker frailty.

[Figures 3 & 4 about here]

[10] Linear correlations shown in Table 2 clearly underestimate the actual differences in slopes between Barker and background mortality due to the non-linear pattern, but they still show flatter curves under the Barker regime.

[Tables 1 & 2 about here]

5 Summary, discussion and extensions

We propose a model for mortality patterns with discrete Barker frailty and Barker effects. We show, mathematically and via simulations, that a mortality regime with declining mortality and discrete Barker frailty will experience a stronger decelerating force than when only standard frailty prevails. As mortality declines, the selection pressure of standard frailty weakens over time and works against a sustained rate of mortality decline. Barker frailty augments the force opposing mortality decline with excess mortality among those who, having been exposed to adverse early life conditions, manifest Barker effects upon attaining adult ages. Our formulation reconciles standard frailty with Barker frailty as survivors to critical ages become a 'newly born' cohort at that age that experiences mortality rates with standard frailty and mortality multiplier $R\delta$ (rather than δ)(Vaupel et al. 1979; Vaupel and Yashin 1987; Vaupel and Missov 2014; Aalen 1988; Steinsaltz and Wachter 2006).

A regime of declining mortality with Barker frailty exhibits a distinct dynamic. First, while standard frailty leads to progressive attenuation of the slope of adult mortality rates at older ages, Barker frailty can produce unequal levels of attenuation over time.

Second, when background mortality declines, average adult mortality could declines more slowly than background mortality rates, remain steady, or even increase. This leads to non-linear dynamics as the manifestation of excess adult mortality implied by Barker frailty undermines its sustained operation in a mortality regime.

Barker regimes regulated by random critical ages produce more subdued consequences than those with fixed critical ages. This is because in the latter case all individuals who are susceptible

to express Barker frailty do so. Instead, when critical ages vary, individuals susceptible to Barker frailty can only express it after attaining the critical age they are endowed with, not before. This reduces the pool of individuals who can oppose resistance to mortality decline at ages under x, exerting a force equivalent to what would be experienced if excess mortality associated with Barker frailty were reduced.

The simulation confirms inferences derived formally. We single out two fundamental results with important implications for interpretation of empirical patterns and extant mortality theories:

i. *Rates of change of mortality rates over time or the nature of secular mortality decline:* any secular mortality decline regime with standard frailty will experience deceleration of the rate of mortality decline. If, in addition, Barker frailty and effects are non trivial, the rate of deceleration will be augmented and particularly so at older ages. The force of the deceleration will be age and time dependent: the rate of mortality decline will oscillate over time and the size of the oscillations will vary with age. The magnitude of the deceleration will attain a maximum at ages closer to the mean of the critical ages and somewhere in the middle of the period of secular decline. The implication of this result for empirical research is important: in particular, observed oscillations of the rate of change of the force of mortality over time at various ages cannot be mechanically interpreted as outcomes of shifts in the determinants of mortality decline since they can be completely accounted for by the dynamic of Barker frailty.

ii. *The adult mortality slope or the rate of senescence*: any secular mortality decline regime with standard frailty will experience deceleration of the adult mortality slope or rate of senescence. If, in addition, Barker frailty and effects are strong, the rate of increase of mortality with age at adult ages will decrease and do so with varying strength at different ages and times during

the mortality decline. The implication of this is that in mortality regimes with Barker frailty and Barker effects standard interpretations of time trends of the age-dependent rates of adult mortality increase could be incorrect as they may be influenced by the changing composition of cohorts by Barker frailty.

Importantly, Barker effects will not be observable in all countries, and their impact will depend on whether or not the populations meet the conditions defined in section 2.2. Thus, the impact of Barker effects on adult life expectancy is more likely to be observed in countries that experienced mortality declines that were at least partially sustained by the diffusion of medical technology rather than by amelioration of standards of living. 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 impact of Barker effects on health and mortality is similar to (but distinct from) pleitropic effects and mutation accumulation, two views about mechanisms of senescence that involve complex interactions between early and late life through the operation of deleterious alleles with differential impact on early and late life (Williams 1957; Finch and Kirkwood 2000; Silvertown 2013; Medawar 1952; Charlesworth 2001). The imprints on human mortality patterns left by these mechanisms has been modeled recently using more general mathematical models that the simple ones we use here (Wachter et al. 2013, 2014). However, the dynamic of Barker effects has important peculiarities that should be reflected in any formal representation. First, unlike the dynamic inherent in pleiotropy and mutation accumulation, Barker effects can have potent deleterious effects early on in life and

thus reduce or suppress altogether their manifestation late in life. Although we did not model these directly (but see the general formulation in the Appendix), any general model for Barker effects should at least be flexible enough to integrate them. Second, the expression and size of effects due to DOHaD, Barker mechanisms and, in particular, PAR are strongly modulated by the interaction between individual propensities, Barker frailty, and environmental (not genetic) conditions encountered in early life. Third, observation of Barker effects is tightly linked with the nature of mortality decline to which susceptible cohort members are exposed. These complex interactions with environments and demographic regimes are not part of the current models for pleiotropic or mutation accumulation effects.

The framework proposed in this paper can be extended in several directions. First, to show its utility as a tool to interpret real phenomena one can translate selected relations embedded in the model(s) into predicted outcomes and design feasible empirical tests involving population data to verify such predictions. Second, the models are flexible enough and admit a number of generalizations. Thus, one could establish a better connection between each of the variants of developmental origins theories and the formal models that represent effects. For example, the nature of critical ages is likely to be different when PAR mechanisms are dominant than when contraction of early infections has more powerful effects. Suitable functional forms to represent critical ages could be deduced from predictions derived from the theories themselves rather than imposed *ex ante*, as we did here. Similarly, the magnitude of excess adult mortality implied by Barker frailty should be specified in accordance to the types of chronic illnesses known or suspected to be influenced by adverse effects of early conditions. Excess adult mortality is almost certainly not age-invariant and its level and age patterns might be tightly linked to the sources of delayed effects

Furthermore, and as suggested by researchers working on senescence (Finch 2007), adverse early conditions may affect the rate of senescence. If so, our models should impose random effects on the *slope* of adult mortality, not just on its level as is normally assumed (Beltrán-Sánchez et al. 2012). This adds a new layer of complexity since the adult mortality slope will be altered both as an artifact of standard and Barker frailty and due to direct effects of adverse early conditions and mortality decline.

Finally, there is a burgeoning literature (Kuzawa and Eisenberg 2014; Gluckman and Hanson 2006; Bateson and Gluckman 2011) showing that the expression of poor early conditions may implicate germ cells and, if so, the risk of adult manifestation of early conditions is passed on from one generation to the next. The models proposed here 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.

References

Aalen, O. O. (1988), "Heterogeneity In Survival Analysis," *Statistics in Medicine*, 7, 1121–37.

Barker, D. J. P. (1998), *Mothers, babies, and health in later life*, Edinburgh; New York: Churchill Livingstone, 2nd ed.

Barouki, R., Gluckman, P. D., Grandjean, P., Hanson, M., and Heindel, J. J. (2012), "Developmental origins of non-communicable disease: implications for research and public health," *Environmental Health*, 11, 10–1186.

Bateson, P. and Gluckman, P. (2011), *Plasticity, robustness, development and evolution*, Cambridge: Cambridge University Press.

Beltrán-Sánchez, H., Crimmins, E. M., and Finch, C. E. (2012), "Early cohort mortality predicts the rate of aging in the cohort: A historical analysis," *Journal of Developmental Origins of Health and Disease*, 3, 380–386.

Bengtsson, T. and Lindström, M. (2000), "Childhood misery and disease in later life: The effects on mortality in old age of hazards experienced in early life, southern Sweden, 1760-1894," *Population Studies*, 54, 263–277.

Charlesworth, B. (2001), "Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing," *Journal of Theoretical Biology*, 210, 47–65.

Crimmins, E. M. and Finch, C. E. (2006), "Infection, inflammation, height, and longevity," *Proc Natl Acad Sci U S A*, 103, 498–503.

Danesh, J., Whincup, P., Walker, M., Lennon, L., Thomson, A., Appleby, P., Gallimore, J. R., and Pepys, M. B. (2000), "Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses," *BMJ*, 321, 199–204.

Devaraj, S., Hemarajata, P., and Versalovic, J. (2013), "The human gut microbiome and body metabolism: implications for obesity and diabetes," *Clinical chemistry*, 59, 617–628.

Elo, I. T. and Preston, S. H. (1992), "Effects of Early-Life Conditions on Adult Mortality: A Review," *Population Index*, 58, 186–212.

Finch, C. (2007), *The biology of human longevity: inflammation, nutrition, and aging in the evolution of life spans*, Burlington, MA: Academic Press, 1st ed.

Finch, C. and Kirkwood, T. (2000), *Chance, Development and Aging*, New York: Oxford.

Finch, C. E. and Crimmins, E. M. (2004), "Inflammatory exposure and historical changes in human life-spans," *Science*, 305, 1736–9.

Fong, I. W. (2000), "Emerging relations between infectious diseases and coronary artery disease and atherosclerosis," *Canadian Medical Association Journal*, 163, 49–56.

Forsdahl, A. (1977), "Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease?" *British Journal of Preventive & Social Medicine*, 31, 91–95.

— (1978), "Living conditions in childhood and subsequent development of risk factors for arteriosclerotic heart disease. The cardiovascular survey in Finnmark 1974-75." *Journal of Epidemiology and Community Health*, 32, 34–37.

Giongo, A., Gano, K. A., Crabb, D. B., Mukherjee, N., Novelo, L. L., Casella, G., Drew, J. C., Ilonen, J., Knip, M., Hyöty, H., et al. (2011), "Toward defining the autoimmune microbiome for type 1 diabetes," *The ISME journal*, 5, 82–91.

Gluckman, P. D. and Hanson, M. A. (2006), *Developmental origins of health and disease*, Cambridge; New York: Cambridge University Press.

Kuzawa, C. W. and Eisenberg, D. T. A. (2014), "The long reach of history: intergenerational and transgenerational pathways to plasticity in human longevity," in *Sociality, Hierarchy, Health: Comparative Biodemography*, eds. Weinstein, M. and Lane, M., Washington D.C. National Research Council Press, book section 4, pp. 65–94.

Langley-Evans, S. C. (2004), *Fetal nutrition and adult disease: programming of chronic disease through fetal exposure to undernutrition*, Frontiers in nutritional science, Wallingford, Oxfordshire, OX; Cambridge, MA: CABI Pub.

Lundborg, P. (2008), "The Health Returns to Education-What can we learn from Twins?" *Institute for the Study of Labor (IZA): Discussion Paper 3399*.

Madsen, M., Andersen, A.-M. N., Christensen, K., Andersen, P. K., and Osler, M. (2010), "Does educational status impact adult mortality in Denmark? A twin approach," *American Journal of Epidemiology*, kwq072.

McDade, T. W. and Kuzawa, C. W. (2004), "Fetal programming of immune function: the early origins of immunity in Filipino adolescents," in *Fetal nutrition and adult disease: programming of chronic disease through fetal exposure to undernutrition*, ed. Langley-Evans, S. C., Wallingford, Oxfordshire, OX ; Cambridge, MA: CABI Pub., Frontiers in nutritional science, book section 13, pp. 311–332.

Medawar, P. (1952), *An Unsolved Problem in Biology*, London: Lewis.

Painter, R. C., Roseboom, T. J., Bossuyt, P. M., Osmond, C., Barker, D. J., and Bleker, O. (2005), "Adult mortality at age 57 after prenatal exposure to the Dutch famine," *European journal of epidemiology*, 20, 673–676.

Palloni, A. and Beltrán-Sánchez, H. (2015a), "Demographic consequences of Barker frailty," in *Dynamic Demographic Analysis*, ed. Schoen, R., Springer, book section 8, pp. 147–176.

— (2015b), "Dynamics of adult mortality regimes with delayed effects," *under rewiew*.

Palloni, A. and Souza, L. (2013), "The fragility of the future and the tug of the past: Longevity in Latin America and the Caribbean," *Demographic Research*, 29, 543–578.

Roseboom, T. J., Van Der Meulen, J. H., Ravelli, A. C., Osmond, C., Barker, D. J., and Bleker, O. P. (2001), "Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview," *Molecular and cellular endocrinology*, 185, 93–98.

Silvertown, J. (2013), *The Long and the Short of It*, The university of Chicago Press.

Steinsaltz, D. R. and Wachter, K. W. (2006), "Understanding mortality rate deceleration and heterogeneity," *Mathematical Population Studies*, 13, 19–37.

Vaupel, J. W., Manton, K. G., and Stallard, E. (1979), "Impact of Heterogeneity in Individual Frailty on the Dynamics of Mortality," *Demography*, 16, 439–454.

Vaupel, J. W. and Missov, T. (2014), "Unobserved population heterogeneity: A review of formal relationships," *Demographic Research*, 31, 659–686.

Vaupel, J. W. and Yashin, A. I. (1987), "Repeated Resuscitation - How Lifesaving Alters Life-Tables," *Demography*, 24, 123–135.

Wachter, K. W., Evans, S. N., and Steinsaltz, D. R. (2013), "The age-specific force of natural selection and biodemographic walls of death," *Proceedings of the National Academy of Sciences*, 110, 10141–10146.

Wachter, K. W., Steinsaltz, D. R., and Evans, S. N. (2014), "Evolutionary shaping of demographic schedules," *Proceedings of the National Academy of Sciences, USA*, 111, 10846–10853.

Williams, G. (1957), "Pleiotropy, natural selection and the evolution of senescence," *Evolution*, 11, 398–411.

Table 1: Estimated correlation coefficient for the relationship between Gompertz slope of a cohort and the level of infant mortality experienced by the same cohort

	Births with Barker:10%		Births with Barker:20%		Births with Barker:30%		Births with Barker:40%	
	Excess mortality from age 40							
	1.5	4.0	1.5	4.0	1.5	4.0	1.5	4.0
				Age 40				
Barker	-0.99	0.91	-0.99	0.93	-0.99	0.93	-0.99	0.93
Background	-0.09	-0.09	-0.09	-0.09	-0.09	-0.09	-0.09	-0.09
				Age 50				
Barker	-0.97	0.95	-0.98	0.97	-0.99	0.97	-0.99	0.99
Background	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28
				Age 60				
Barker	-0.84	0.97	-0.93	0.98	-0.96	0.98	-0.97	0.99
Background	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11
				Age 70				
Barker	0.89	0.96	0.75	0.97	0.08	0.98	-0.71	0.98
Background	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16

Note: Values computed from Figure 3.

Table 2: Estimated correlation coefficient for the relationship between cohort's mortality rates in three different adult age groups and its correspondent infant mortality

	Births with Barker:10%		Births with Barker:20%		Births with Barker:30%		Births with Barker:40%	
	Excess mortality from age 40							
	1.5	4.0	1.5	4.0	1.5	4.0	1.5	4.0
				${}_{10}Q_{50}$				
Barker	1.000	0.999	1.000	0.999	1.000	0.999	1.000	0.999
Background	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
				${}_{10}Q_{60}$				
Barker	0.999	0.998	0.999	0.998	0.999	0.997	0.999	0.996
Background	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
				${}_{10}Q_{70}$				
Barker	0.994	0.994	0.993	0.993	0.993	0.993	0.992	0.993
Background	0.994	0.994	0.994	0.994	0.994	0.994	0.994	0.994

Note: Values computed from Figure 4.

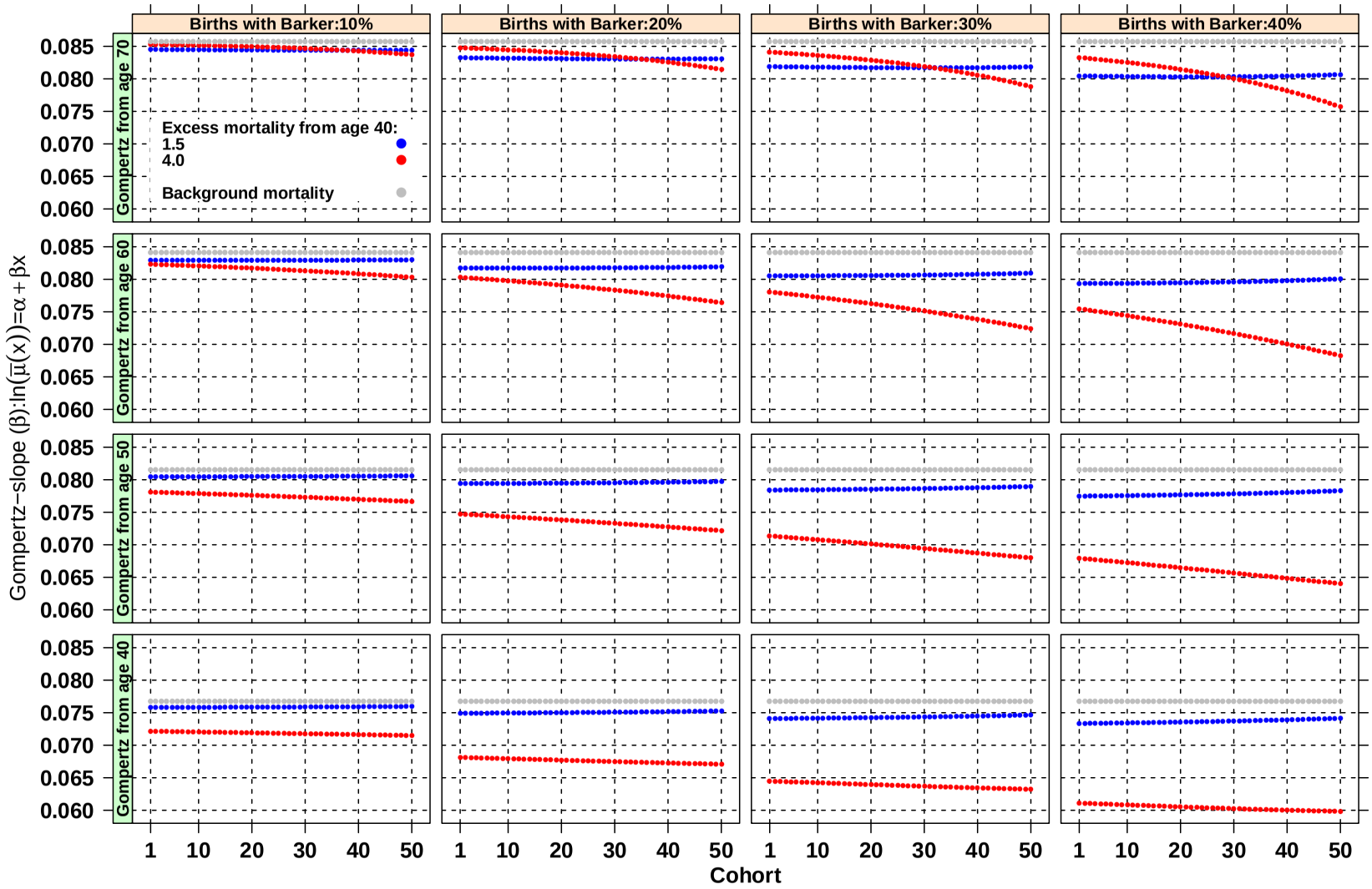

Figure 1: Estimated slopes of adult mortality by birth cohort for populations with different levels of prevalence of Barker frailty and by lowest bound of age considered in the estimation of the adult mortality slope (40, 50, 60 and 70).

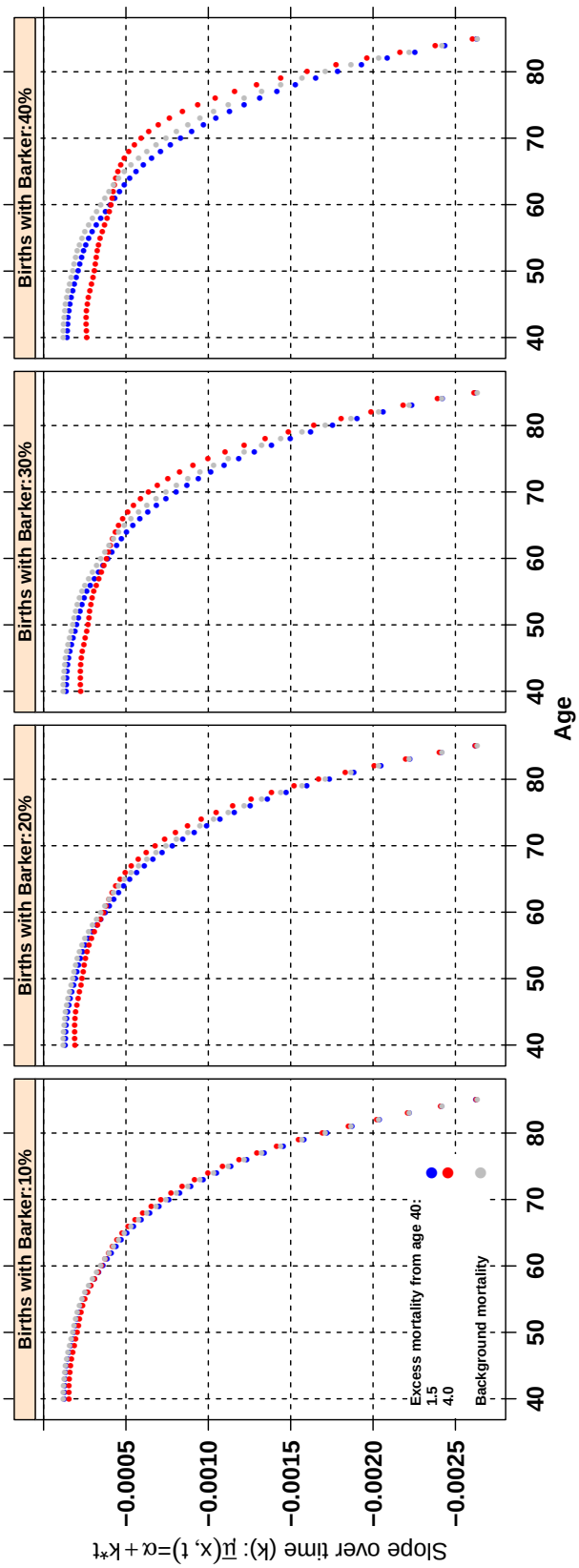

Figure 2: Average rate of mortality decline by adult age separately by levels of prevalence of Barker frailty.

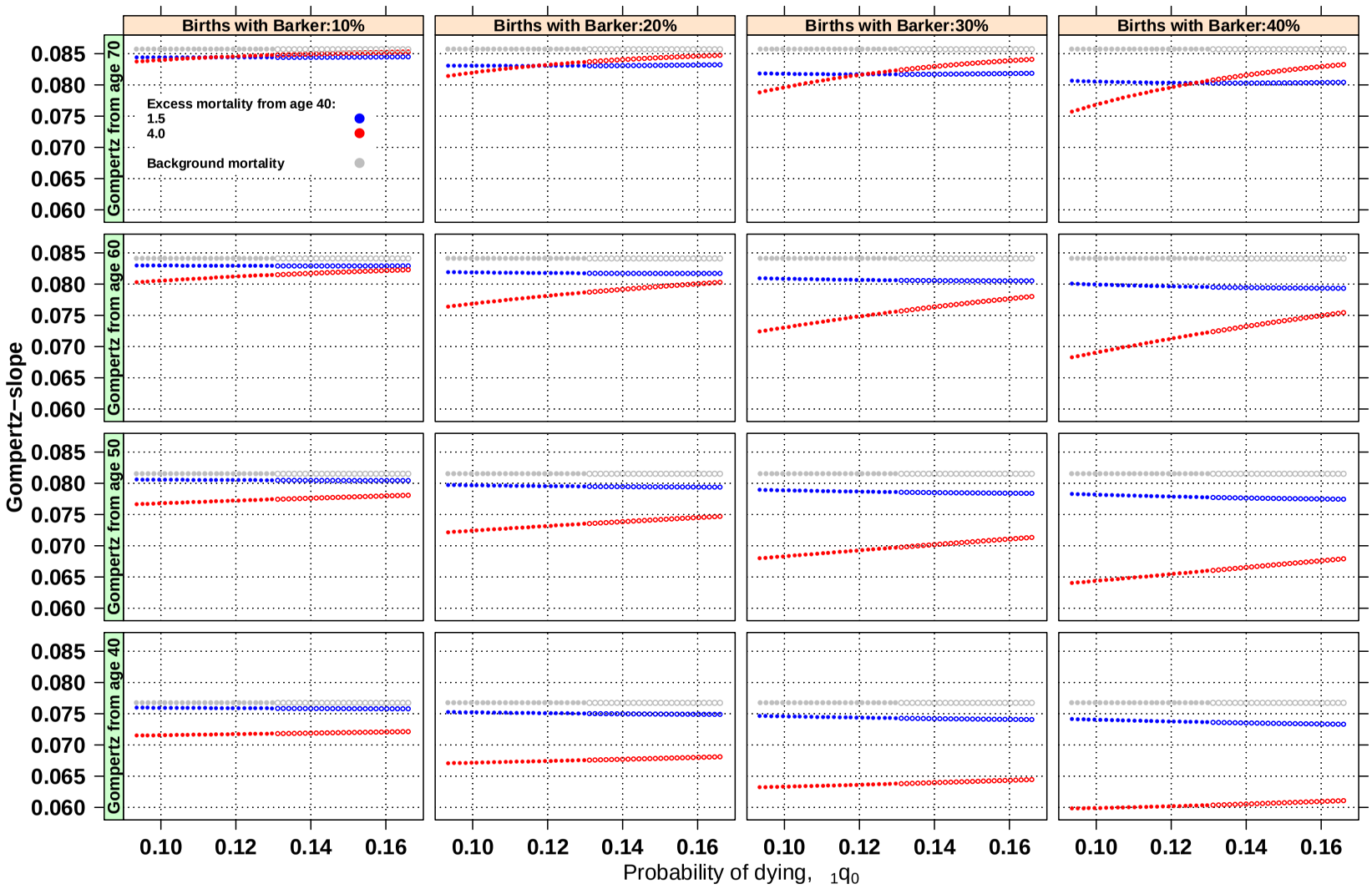

Figure 3: Estimated Gompertz slope of a cohort and the level of infant mortality experienced by the same cohort.
Note: Open circles represent older cohorts (i.e.,those born in the early stages of the mortality decline) and closed circles correspond to recent cohorts.

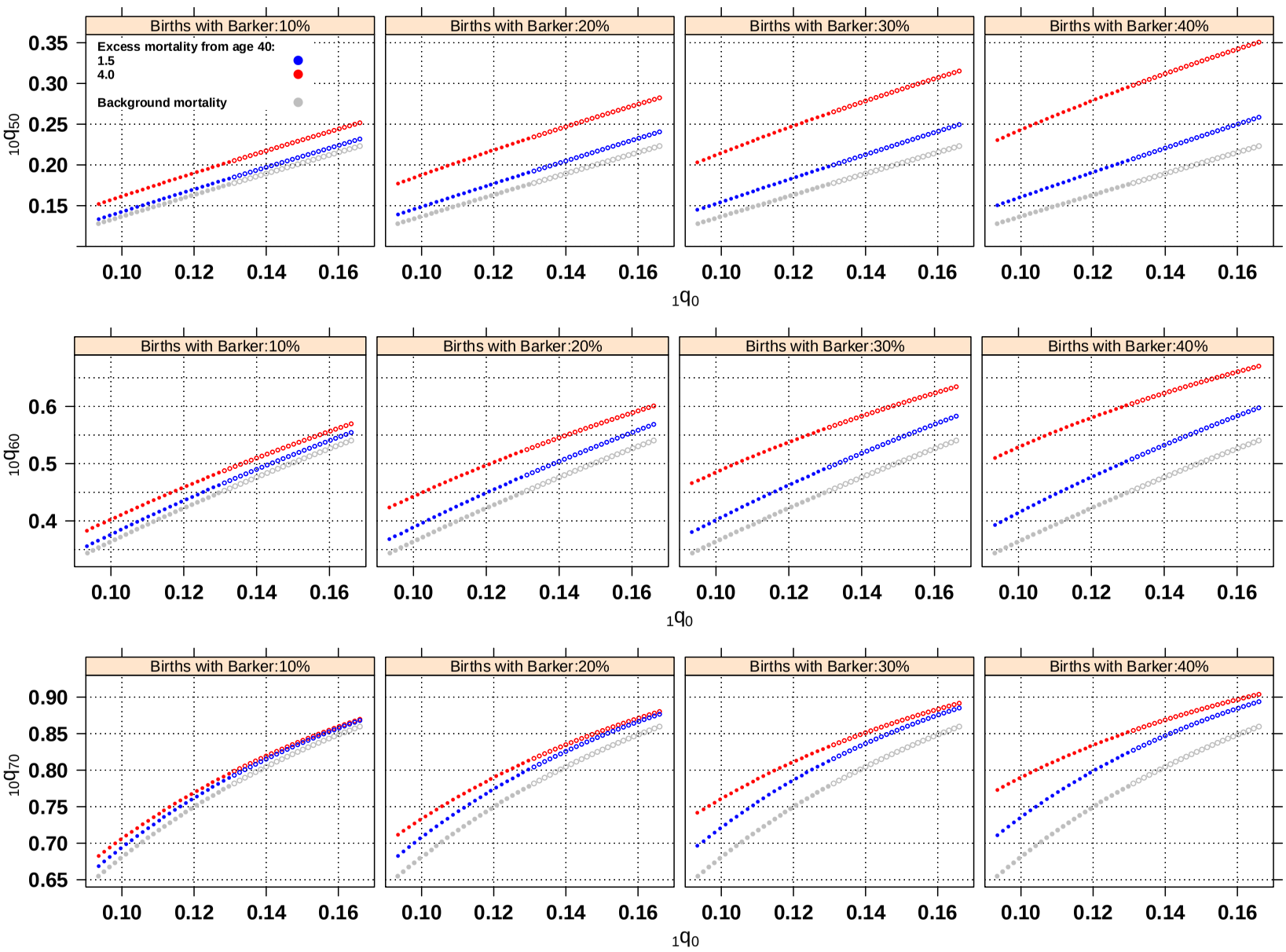

Figure 4: Cohort's mortality rates in three different adult age groups and its correspondent infant mortality.
Note: Open circles represent older cohorts (i.e.,those born in the early stages of the mortality decline) and closed circles correspond to recent cohorts.

APPENDIX
Discrete Barker frailty and warped older age mortality dynamics*

Alberto Palloni† Hiram Beltrán-Sánchez‡

Abstract

We develop a discrete variant of a general model for adult mortality influenced by the delayed impact of early conditions on adult health and mortality. The discrete variant of the model builds on an intuitively appealing interpretation of conditions that induce delayed effects and is an extension of the discrete form of the standard frailty model with distinct implications. We show that introducing delayed effects is equivalent to perturbing adult mortality patterns with a particular class of time(age)-varying frailty. We emphasize two main results. First, populations with delayed effects could experience unchanging or increasing adult mortality even when background mortality has been declining for long periods of time. Although this phenomenon also occurs in a regime with standard frailty, the distortions can be more severe under a regime with Barker frailty. As a consequence, conventional interpretations of the observed rates of adult mortality decline in societies that experience Barker frailty may be inappropriate. Second, the observed rate of senescence (slope of adult mortality rates) in populations with delayed effects could increase, decrease or remain steady over time and across adult ages even though the rate of senescence of the background age pattern of mortality is time and age invariant. This implies that standard interpretations of empirical estimates of the slope of adult mortality rates in populations with delayed effects may be misleading since they can reflect mechanisms other than those inducing senescence as conventionally understood in the literature.

1 General model with fixed critical ages and constant mortality

Assume the existence of a trait, $\delta > 1$, acquired as early as during conception and gestation, that signals the net propensity of individuals to express Barker effects. A general discrete representation of the effects of the trait on the mortality pattern of a population is the following:

$$\mu_i(y) = \begin{cases} \mu_s(y)((1 - I_i) + I_i\theta) & \text{for } y < Y_0, \\ \mu_s(y) & \text{for } Y_0 \leq y < Y_1, \\ \mu_s(y)((1 - I_i) + I_i R(\delta_i, y)) & \text{for } Y_1 \leq y, \end{cases}$$

where I_i is a random indicator function attaining the value 1 if $\delta_i > \delta_0$ and 0 otherwise, δ_0 is a threshold Barker frailty value for excess mortality, θ is excess mortality at ages younger than Y_0 and

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†Center for Demography of Health & Aging, University of Wisconsin-Madison. Email: palloni@ssc.wisc.edu.

‡Department of Community Health Sciences at the Fielding School of Public Health & California Center for Population Research, both at UCLA. Email: beltrans@ucla.edu

$R(\delta_i, y)$ is a function of both age and the trait δ that determines the magnitude of Barker delayed effects on adult mortality, e.g. the value of Barker effect when $y > Y_1$.[1] The average mortality rate in each age segment will be:

$$\bar{\mu}(y) = \begin{cases} \mu_s(y)\left[\dfrac{\theta + D_0(y)}{1 + D_0(y)}\right] & \text{for } y < Y_0, \quad (1.1) \\ \mu_s(y) & \text{for } Y_0 \leq y < Y_1, \\ \mu_s(y)\left[\dfrac{E_y(R(\delta, y)|\delta > \delta_0) + D_1(y)}{1 + D_1(y)}\right] & \text{for } Y_1 \leq y, \quad (1.2) \end{cases}$$

and

$$D_0(y) = [\exp(-(1-\theta)\Lambda_s(0,y))]\left[\frac{1-\psi(\delta_0)}{\psi(\delta_0)}\right]$$
$$D_1(y) = [\exp(-(1-\tau)\Lambda_s(0,y))]\left[\frac{1-\psi(\delta_0)}{\psi(\delta_0)}\right]$$

where $\psi(\delta_0)$ is the probability at birth of $\delta > \delta_0$, $\Lambda_s(0, y)$ is the integrated hazard between ages 0 and y in the baseline mortality pattern, and τ is the ratio of the integrated hazard from age 0 to age y corresponding to the *expected value* of the survival function among those with $\delta > \delta_0$ to the integrated hazard in the baseline mortality pattern. The expressions within the squared parentheses in (1.1) and (1.2) are weighted averages of the mean excess mortality in the sub-population with $\delta > \delta_0$, θ in equation (1.1) and $E_y(R(\delta, y)|\delta > \delta_0)$ in equation (1.2), and among those with $\delta \leq \delta_0$, in both equations. The weights are $D_0/(1 + D_0)$ and $D_1/(1 + D_1)$ in (1.1) and (1.2) respectively, both functions of the survival probabilities to age y and of the original fraction of individuals who are candidates to express Barker frailty.

The precise definition of $R(\delta, y)$ should reflect considerations regarding the nature of delayed effects. Elsewhere (Palloni and Beltrán-Sánchez 2015) we proposed a function with appealing features and define $R(\delta_0, y) = \alpha_0 + I_i(\alpha_1(y - Y_1) + \alpha_2(\delta - \delta_0))$ with $\alpha_0 \geq 1$, $\alpha_1 > 0$, and $\alpha_2 > 0$. This function implies that individuals who carry values of Barker frailty over δ_0 are penalized with increases in excess adult mortality as they age above the critical age Y_1 as well as due to departures from the threshold value δ_0. There are, of course, other plausible candidate functional forms but we have insufficient theoretical rationale to justify or choose among them, all complicate the algebra of the model, and in all cases their effects on empirical mortality patterns may be difficult to identify.

To summarize: the general discrete model captures a number of important features. First, Barker frailty is a random trait acquired early in life and influencing mortality at all ages but specially during early childhood and at adult ages. Second, there are critical ages Y_0 and Y_1 below and above which Barker frailty expresses itself as excess mortality risks (Barker effects). Third, excess mortality risks can change after attaining the critical age Y_1 and could do so as a function of the level of Barker frailty. This feature implies that survivors at older ages who express Barker frailty will experience effects whose magnitude depends on their level of vulnerability and on aging itself.

[1] In a recent paper Vaupel and Missov (2014) propose an age dependent effect of standard frailty 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.

2 Expression for $P_B(y,t)$

The quantity $P_B(y,t)$ and its time and age derivatives are the following:

$$\begin{aligned} P_B(y,t) &= \frac{1}{1+h\ \exp(-k(t)(1-\lambda_B)\phi_s(y))} \\ \frac{\partial P_B(y,t)}{\partial t} &= -\frac{\partial(k(t))}{\partial t}\left[\phi_s(y)(\lambda_B-1)\pi(y,t)\right] > 0 \\ \frac{\partial P_B(y,t)}{\partial y} &= -k(t)\mu_s(y)(1-\lambda_B)\pi(y,t) < 0 \end{aligned}$$

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

3 Expression for $P_B^1(y,t)$

This quantity can be approximated as

$$P_B^1(y,t) \simeq \left[1+\exp(-k(t)(1-\lambda_B)\Lambda_S(\check{y},y))\left(\frac{1-\Phi_Z(y)}{\Phi_Z(y)}\right)+\frac{h}{\Phi_Z(y)}\right]^{-1}$$

with $\Lambda_S(\check{y},y) = \int_{\check{y}}^{y} \mu_s(v)dv$ and $40 \leq \check{y} \leq y$ is the (conditional) mean of the critical ages z among those with Barker frailty who survive to age y.

4 Simulation of mortality regimes

To evaluate the magnitude of Barker effects and to gain insights on the relations described above, we simulate a series of cohorts undergoing a secular mortality decline and expose them to several variants of discrete Barker frailty, with fixed and random critical ages. The objective of the simulations is to shed light on the behavior of two functions, the age-specific rates of mortality change and the adult mortality slope across birth cohorts.

The simulation design is according to the following rules:

1. We simulate 50 cohorts born between 1950 to 2000 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 age-specific mortality rates after 100 years correspond to a life table with a life expectancy at birth of 90 years (i.e., cohort specific life expectancy at birth more than doubles during a century).

2. For each birth cohort we create 300 copies and each of these copies has a random frailty value, $(1+\delta)$, where δ is drawn from a distribution $Gamma(r,\lambda)$ with $r = 1$ and $1/\lambda = 4$.[2] We then create two regimes, one with a fixed and one with an increasing proportion of births who can express Barker frailty. In the fixed regime we determine who will express Barker by generating two subgroups: one with $1+\delta > G$ and the other with $1+\delta \leq G$ where G changes from 0.10 to 0.40 in increments of 0.10. In the time changing regime we set parameters so that G increases from a low value of 0.10 applicable to the oldest birth cohort to a high value of 0.40 for the youngest birth cohort in linear fashion.

[2] 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.

3. We assume two regimes of critical ages. The first is a regime with fixed critical age equal to 40 ($Y_1 = 40$) after which manifestation of early damage begins to take place in the form of excess mortality risk ($R > 1$). The second regime allows random critical ages. Each copy of a cohort is assigned a critical age $Z = 40 + u$ where u is drawn from a gamma distribution with mean and standard deviations equal to 10 and a coefficient of variation equal to 1.

4. The size of Barker effects or excess mortality, R, ranges from 1.5 to 4 in increments of 0.5. Thus, in both the regime with fixed and with random critical ages we will have a total of 5x6=30 variants of 50 cohorts each (each of these containing 300 copies).

5. Each of the $i = 1, \ldots, 300$ copies of cohorts contained in the 30 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, the mean mortality rate ($\bar{\mu}(y)$) across all 300 copies, the mean adult mortality slope above ages 45, 55, 65 and 75 and the numerical first and second derivatives of the average mortality rates.

References

Coale, A. J. and Demeny, P. (1983), *Regional model life tables and stable populations*, Princeton; New Jersey: Princeton Univ. Press, 2nd ed.

Palloni, A. and Beltrán-Sánchez, H. (2015), "Demographic consequences of Barker frailty," in *Dynamic Demographic Analysis*, ed. Schoen, R., Springer, book section 8, pp. 147–176.

Vaupel, J. W. and Missov, T. (2014), "Unobserved population heterogeneity: A review of formal relationships," *Demographic Research*, 31, 659–686.