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Insights into mortality patterns and causes of death through a process point of view

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Abstract

Process point of view models of mortality such as the Strehler-Mildvan-Gompertz and stochastic vitality models, represent death in terms of abstract loss of survival capacity through challenges and dissipation. Drawing on hallmarks of aging, we link these abstract concepts to candidate biological mechanisms through a framework that partitions causes of death into distal and proximal components. Hypothesizing that the immune system is a mortality nexus, we define distal components for juvenile immune system development and adult immunosenescence. Immune system disruption by proximal components defines three cause-of-death classes: juvenile extrinsic mortality and adult extrinsic mortality result from extrinsic disease and stress challenges to the juvenile and adult stages of the immune system, and adult intrinsic mortality results from the exhaustion of the adult immune system by immunosenescence. Patterns of model parameters, generated from Swedish mortality data (1751-2010), exhibit biologically meaningful correspondences to economic, health and cause-of-death patterns. The 20th century epidemiological transition in mortality is characterized by the proximal component shifting from infectious disease challenges to physical exertion challenges. The distal component change, involving slow improvements in immune system function, was of secondary importance. Extensions and limitations of a distal/proximal framework for characterizing more explicit causes of death, e.g. the young adult mortality hump or cancer in old age are discussed. Finally, our intent is to demonstrate that new insights into historical and future patterns of mortality can be gained through a process point of view.

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INTRODUCTION

The vast majority of models that characterize historical patterns of mortality and project future trends are based on age and time dependent changes in the rate of mortality (Booth and Tickle 2008). Such models disregard the underlying processes leading up to the mortality event and are therefore ill-equipped to treat the interactions of proximal (i.e. acute) and distal (i.e. chronic) causes of death (COD). Cause-specific mortality rate projections, which assume independent causes of mortality, over predict combined mortality (Alai et al. 2015), and projecting future mortality trends based on historical trends is problematic when the underlying COD change over history (Tuljapurkar 1998). An alternative modeling approach, which takes the process point of view (Aalen and Gjessing 2001), has properties that in principle are better equipped to address the proximal and distal interactions of COD and therefor offers a possible way forward in understanding causes of historical trends in mortality and forecasting future trends.

Process point-of-view models have been developed in two distinct approaches. The early approach treats mortality as random extrinsic challenges exceeding a linearly declining measure of survival capacity, denoted vitality (Strehler and Mildvan 1960). The more recent approach treats mortality as the passage of stochastically declining vitality from an initial value at birth or some prescribed age into a zero-vitality boundary representing death (Steinsaltz and Evans 2004). The approaches have been combined in a mathematically tractable two-process model (Li and Anderson 2013) that characterizes mortalities from extrinsic challenges to vitality and passage of vitality into the zero boundary, which we also refer to as intrinsic challenges. Although a number of insights have been obtained by considering the processes individually or together (Anderson 2000; Li and Anderson 2013; Li and Anderson 2015; Sharrow and Anderson 2016; Sharrow and Anderson *in press;* Strehler and Mildvan 1960; Stroustrup et al. 2016; Weitz and Fraser 2001) these applications have been vague on the biological meaning of vitality and how challenge events result in mortality. If such models are to be of value in understanding and forecasting mortality patterns, their underlying biological foundations must be better established (Steinsaltz and Evans 2004).

The goal of this paper is to advance the process point of view by identifying biological processes underlying the framework. We first review cellular and physiological mechanisms of aging and mortality and highlight the vitality-like properties. Second, we discuss leading COD in this framework, emphasizing the importance of proximal processes in COD classifications. Third, we include a juvenile mortality component in the two-process vitality model and propose biological mechanisms underlying each of the model terms. Fourth, we fit the model to the 250-year Swedish mortality data and discuss the trends of the model coefficients and mortality components in terms of historical changes in environmental, social and health factors.

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BIOLOGICAL PROCESSES UNDERLYING VITALITY

Properties of the vitality framework

To explore a biological basis for a process point-of-view model we first note the features of the vitality framework. The original two-process model (Li and Anderson 2013) comes from a classification of mortality into two types; an extrinsic mortality that is avoidable and an intrinsic mortality that is unavoidable (Carnes and Olshansky 1997). Here we refine the concept and distinguish mortality in terms of distal and proximal components. The distal component, vitality, represents processes leading up to the mortality event and a proximal component represents the immediate cause of the death. In the framework, the distal component is defined by the initial vitality level and its rate of change. The proximal component takes two forms. An extrinsic form is mathematically represented by random environmental challenges to the remaining vitality. An intrinsic form is mathematically represented by the stochastic passage of vitality into the zero-vitality boundary. Both intrinsic and extrinsic events trigger the loss of homeostasis and the onset of death. In this framework, COD is classified according to both proximal and distal components. For example, death from pneumonia in young and old age persons can be classified as different COD. Both age groups share the same proximal challenge, pneumonia, but have different distal components. In young age, the distal component represents a weak, but developing, immune system while in old age the distal component represents a weak and declining immune system. The distinction is important because the immune system is significantly different in each example, which affects the disease etiology as well as its treatment (McCabe et al. 2009; Rudan et al. 2008) and vaccination strategies (Westerink et al. 2012).

To establish a stronger biological foundation for the process point of view we briefly review aging processes from the perspective of the cell, the network and the principal physiological system of aging, the immune system. Our goal is to highlight vitality-like properties at each scale and use these analogies to guide the interpretation of the vitality framework. Our goal is not to claim specific correspondences between aging mechanisms and the model parameters, such a quest is quixotic. Aging is complex, the theories are numerous (Medvedev 1990) and in flux because of the rapidly advancing research in longevity (e.g. Gems and Partridge 2013; Kenyon 2010; Wensink et al. 2016). However, simple models successfully characterize the major pattern of mortality and attempts to explain observed deviations from the pattern have led to significant insights into the mortality processes (e.g. Li and Anderson 2015; Yashin et al. 2001; Zheng et al. 2011). Thus, our goal here is to identify plausible candidate processes underlying the vitality framework, and through a comparison of the processes and the model, highlight some challenges and limitations of the process point of view.

Cellular hallmarks of aging

At the molecular and cellular levels, nine hallmarks of aging have been identified and placed into three hierarchical groups (López-Otín et al. 2013). The first group involves damage of the cellular processes (genomic instability, epigenetic alterations, telomere attrition, and loss

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of proteostasis). A middle group (deregulation of nutrient sensing, mitochondrial dysfunction, and cellular senescence) are compensatory responses to damage that mitigate acute damage but can also exacerbate chronic damage. The final group are integrative hallmarks involving effects of the other two groups on tissue homeostasis and function. They include the decline of regenerative potential of stem cells with age and chronic inflammation of tissue (stem cell exhaustion and altered intercellular communication). From the perspective of the vitality framework the properties of the first group of hallmarks are similar to the distal component of mortality, in that as vitality is a declining measure of survival capacity, the processes decline with age reducing the capacity of the cells to maintain homeostasis. The properties of the second and third groups are similar to the proximal component of mortality in that the processes transition to a lower, or nonfunctional state, when the distal processes reach a limit. For example, telomeres, the protective end-caps of chromosomes, are akin to vitality in that they shorten with each cell replication. Cell senescence is akin to vitality boundary passage in that when telomeres reach a critical length the cell enters replicative senescence (Blackburn et al. 2015). In a similar manner autophagy, the process to remove damaged proteins and invasive pathogens in cells, is akin to vitality in that it declines with age by the accumulation of waste material. Analogous to vitality challenges, cells enter apoptosis when the rate of pathogen flux or protein damage exceeds the autophagic capacity (Cuervo et al. 2005; Denton et al. 2015; Han et al. 2015).

Differential aging in regulatory networks

The hallmarks of aging develop stochastically in physiological systems causing different forms of aging. For example, physiological system blood biomarkers (e.g. lipids, leucocytes, oxygen transport, liver, vitamins and electrolytes) exhibited different age-related deviations from the norms and different patterns with causes of death. Notably, cardiovascular disease was predicted by several of the biomarkers but cancer was generally unassociated with any (Li et al. 2015). Additionally, an index of biological markers of aging was a better predictor of mortality risk than an index of activity markers (Cornman et al. 2016). These studies and others suggest that, leading up to death, the dysregulation of the multiple cellular regulatory networks progress in semi-independent patterns (Cohen 2016; Riera et al. 2016). The important point for a vitality framework is the possibility of representing the distal components of COD with separate vitality streams associated with different physiological networks.

Immune system

At the physiological system scale, the majority of research has focused on the immune system, because it is the network of cells, tissues and organs that protect and repair body damage resulting from internal and external stresses and pathogens (Weiskopf et al. 2009). Immune system function involves all of the primary hallmarks of aging (López-Otín et al. 2013). For example, autophagy is the central process of the immune system for engulfing and removing pathogens (Kuballa et al. 2012; Puleston and Simon 2014), telomere attrition limits the ability of the immune system to generate lymphocytes (Aubert and Lansdorp 2008;

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Blackburn et al. 2015) and epigenetics remolding of the chromatin contributes to the age-dependent increase of the immune system inflammatory response (Booth and Brunet 2016). Two aging hallmarks, the gradual deterioration of the immune system, known as immunosenescence (Aw et al. 2007), and chronic low-grade inflammations, known as inflammaging (Franceschi et al. 2007; Frasca and Blomberg 2015), are central actors in determining death due to infections (Weiskopf et al. 2009), cancers (Bonafè et al. 2001; Palucka and Coussens 2016; Vasto et al. 2009), heart disease (Epstein and Ross 1999; Legein et al. 2013) and other diseases (Chung et al. 2009).

For identifying processes underlying vitality, we focus on the cells of the innate and adaptive immune systems and how they change with age. The innate immune system, mainly consisting of monocytes, neutrophils, natural killer and dendritic cells, represents the first line of defense against pathogens. The cells are constantly produced by stem cells in the bone marrow and freely circulate but do not divide. The adaptive immune system consists of B and T cells, which are produced by stem cells in the bone marrow and mature as naïve cells in the bone marrow and thymus respectively. Dendritic cells of the innate immune system present antigens of pathogens to naïve B and T cells, which then clonally divide as effector cells to mount further defense. After an infection is removed a fraction of the effector T cells remain as memory T cells, which are able to quickly respond to future infections (Weiskopf et al. 2009). Both innate and adaptive immune cells engulf and digest the invading pathogen and regulate homeostasis through autophagy (Janeway et al. 2005; Levine and Deretic 2007).

Aging patterns of the immune system

Patterns of mortality over life have been partitioned into two evolutionary-significant stages: ontogenescence, representing the declining mortality rate from conception to maturation and senescence representing the increasing mortality rate from maturation to old age (Levitis 2011). In both stages, robustness is considered a key factor in determining patterns of mortality. In our vitality framework robustness is indexed by vitality and our working hypothesis is that the immune system is the key player. Therefore, we focus here on the contributions of the immune system to ontogenescence and senescence separately.

Ontogenescence

It is well established that fetal and newborn mammals have limited ability to mount immune responses (Holt and Jones 2000). In particular, the limitation involves low innate system activity at birth, making infants susceptible to bacterial and viral infections (Levy 2007). However, the cell levels change rapidly postpartum. Neutrophils and monocytes dominate the innate system at birth and can exceed adult levels before normalizing within a few days. In the adaptive system, both T and B cells numbers are high at birth, increase further over the first year of life and then decrease towards adult levels in school age children. However, memory T cells, a measure of the adaptive system's capacity to respond to infection, are very low at birth but increase steadily to age of 5 and reach adult levels by age of 15 years (Ygberg and Nilsson 2012). In a vitality framework these early life changes can be represented by a separate early life vitality process.

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Immunosenescence

The adult immune system gradually degrades with age through immunosenescence (Gruver et al. 2007; Weiskopf et al. 2009). Degradation is most severe in the adaptive immune system as hallmarked by the decrease in naïve T cells and accumulation of memory T cells. The reduction in naïve T cells is in part driven by reduced bone marrow immune cell output involving the involution of the thymus, where T cells mature. The involution begins at puberty and declines by about 3% per year through middle age, 1% in old age and is barely detectable by age 85 (Palmer 2013). The increase, or inflation, of memory T cells is associated with infections of cytomegalovirus (CMV), which once established, results in an inflation of memory T cells as the immune system tries to contain, but not remove, the infection (Pawelec et al. 2009). In developed countries a significant proportion of the population is CMV-negative, but with age, the population that is CMV-positive increases plateauing at about 85-90% by age 75-80. The prevalence of infection is greater in developing countries where 90% may be infected in youth (Pawelec et al. 2012). CMV infections have been associated with a number of chronic illnesses and markedly increase vascular disease COD in individuals over 65 years of age (Savva et al. 2013) but may have beneficial effects on the immune system in young individuals (Sansoni et al. 2014). Besides contributions of thymus involution and CVM infections to T cell dynamics, immune system degradation also involves interconnected responses of many other processes including epigenetic remodeling of cells, telomere shortening and the diversity of naïve T cell receptors (Ongrádi and Kövesdi 2010).

From the perspective of shaping mortality profiles, the end result of immunosenescence is age-increasing susceptibility to novel infections (Kline and Bowdish 2016). Furthermore, a number of behavioral and environmental factors affect the rate of immunosenescence. A major factor is protein-energy malnutrition in which individuals with insufficient protein in their diet experience atrophy of immune system organs and reduction of immune system leucocytes (Beisel 1996). However, diet restriction that reduces body weight without protein-energy malnutrition can increase immune function (Ritz and Gardner 2006). Obesity is also a factor in immune system function including reduced number and response of T cells and lymphoid atrophy, which result in higher susceptibility to infectious diseases. Furthermore, evidence indicates that response of the immune system to infection diminishes its capacity to respond to future infections (Schaible and Kaufmann 2007). Finally, exercise has been demonstrated to delay or possibly reverse immunosenescence (Turner 2016).

Immunosenescence, as a generic measure of the ability of the immune system to protect the organism, is a central nexus between the biology of aging and vitality. Viewing the rate of loss of vitality as an index of the rate of immunosenescence highlights important features to that need to be considered in extensions of the model. In particular, the rate of change of vitality is population specific and depends on the cumulative experience in terms of past infections and health behavior. These factors can, in principle, be represented as nonlethal challenges that effect vitality loss. In the current form of the model sublethal challenges are subsumed into the mean and variability in the rate of loss of vitality. In other words, in estimating vitality rate parameters we implicitly include the effects of random challenges on

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the rate of loss of vitality. This suggests an interplay of proximal factors, which are nonlethal but contribute to shaping the distal factors of mortality and thus offers a quantitative framework in which to represent the interplay between life history and the patterns of morbidity and mortality in populations.

CAUSE OF DEATH

We consider next how challenge and boundary passage events relate to COD. In particular, using the historical shift in COD from infectious diseases to degenerative diseases and cancers we illustrate that the partition into intrinsic and extrinsic processes of mortality depends on the age of death and the mix of challenge types.

Infectious disease

The patterns of infectious diseases (ID) through human history have been linked to ecological processes including the spatial distribution, movement and nutritional status of populations (Dobson and Carper 1996). Reductions in mortality from infectious disease can be largely reduced to two factors: reductions in disease transmission and host susceptibility (Cohen 2000). In the context of the vitality framework these factors are expressed by three processes: disease transmission is characterized by the frequency of extrinsic challenges, the disease virulence is expressed by the challenge magnitude and host susceptibility is expressed by vitality.

Beginning the 20th century, infectious diseases were the leading cause of death worldwide. In the United States tuberculosis, pneumonia and diarrhoeral disease accounted for ~30% of mortalities while at the end of the century they accounted for less than 5%. This decline is first attributed to reductions in both challenge frequency and magnitude. The frequency reduction involved reduced disease transmission through improved sanitation, hygiene and safer food and water. The magnitude reduction is attributed to the introduction of antimicrobial agents in the mid-20th century. However, in developing countries infectious diseases currently account for ~25% of the deaths (Cohen 2000). Finally, the reduction can be attributed to lower host susceptibility involving a lowering in the rate of immunosenescence as discussed above. However, reduction in the impacts of disease challenges have not mitigated the effects of immunosenescence in old age. In people ≥ 65 years old, one third of the deaths worldwide are from bacterial infections including lower respiratory tract, urinary tract and skin/soft tissue infections (Kline and Bowdish 2016). In this age group about 85% of the deaths are attributed to influenza and pneumonia (Mouton et al. 2001).

To a first order, young individuals experience the same disease challenges as adults, but the mortality rate is patterned by their immune system development that results in the mortality rate declining in an exponential-like manner through childhood. Challenges involving complications during neonatal preterm births and intrapartum together account for 70% of deaths in the first 6 days after birth. In the neonatal stage (~2 to 4 weeks) deaths are primarily

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caused by infections (Heron 2015) and over the first five years of life, infectious disease, including acute respiratory infections, diarrhea and malaria account for about two-thirds of all deaths (World Health Organization 2010). Malnutrition is directly, or indirectly, responsible for half the deaths per year for children under five and malnutrition also worsens the outcome from other infections including tuberculosis, HIV/AIDS and malaria (Schaible and Kaufmann 2007).

Between ~10–25 years of age, the rate of mortality increases mainly from physical injury associated with risky behavior. Known as the early adult mortality hump, globally in 2004 it accounted for an 82% increase of the total mortalities in this age range (Patton et al. 2009). The phenomena involves a mismatch in the rate of development of the neural systems that control reward seeking and risk avoidance behaviors (Shulman et al. 2016). In the vitality framework this increase can be expressed as a transient increase in challenge frequency and magnitude that is superimposed on background challenges involving infections.

In the vitality framework, mortality from infectious disease and physical injury are attributed to random challenges that occur over short periods of time. However, in reality a latency exists between the challenge event and the mortality. The latency can be on the order of weeks for diseases such as typhoid and pneumonia and months to years for tuberculosis (Control and Prevention 2016). The long latency is a result of tuberculosis etiology, which is present without clinical symptoms in one third of the world population (Flynn and Chan 2001). Those with active infections develop active tuberculosis within 1 to 3 years while a third become clinically latent and are not infectious. In ~10% of the latent group the infection can reactivate. Treatment is largely successful but in developing countries approximately 7% of those under treatment die within a few months (Birlie et al. 2015; Field et al. 2014). Tuberculosis illustrates a further challenge in partitioning mortalities because of its protracted development it has been classifies as an underlying cause of death as well as the associated cause of death with other causes being ascribed as the underlying cause (Santo et al. 2003).

In principle, the latency can decrease with lower vitality. However, in the model framework the classification of extrinsic mortality does not depend on disease latency. Instead, the classification depends on the distribution of mortalities with age. A pattern of exponentially increasing mortality with age contributes to the intensity of extrinsic mortality in the model.

Cardiovascular disease

Cardiovascular disease (CVD), the leading COD worldwide (Heron 2015), has properties that cast it into the class of extrinsic mortality. Firstly, CVD exhibits an exponentially increasing mortality rate with age (Example of age distribution of incidence of cardiovascular diseases for female Swedish population 2000-2004 is available from the Institute for Health Metrics and Evaluation at http://ihmeuw.org/3tzc) and its distal and proximal components have clear extrinsic mortality features. For example, atherosclerosis, the accumulation of plaque within the artery wall, becomes the distal component of CVD death while the immediate cause of death, myocardial infractions, become the proximal component. Looking further,

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atherosclerosis is an inflammatory disease promoted by inflammaging and immunosenescence (Epstein and Ross 1999; Legein et al. 2013). A surrogate measure of atherosclerosis, the carotid intima-media thickness, has a log-linear relationship with cardiovascular events (Bots et al. 2016) and studies suggest the thickness increases approximately linearly with age (Polak et al. 2011). Furthermore, telomere length, which is associated with the progression of atherosclerosis, also has a linear relationship with age (Aviv et al. 2015; Haycock et al. 2014). For the proximal component, myocardial infractions are triggered by physical activity, emotional stress, sexual activity and eating (Čulić et al. 2005), which together can be represented by probability distributions of challenge magnitude and frequency. Importantly, the distributions of challenges for CVD and ID are significantly different. CVD challenges have high frequency, essentially occurring daily, but their magnitude is low. In contrast, ID challenges occur with low frequency, on the order of years, but their magnitudes are high. These differences result in ID, when of sufficient frequency, masking the contribution of CVD to extrinsic mortality. This masking effect is discussed below.

Cancer

Malignant neoplasms currently represent the second major COD worldwide (Heron 2015). For many types of cancer the rate of mortality increases approximately exponentially through early-to-middle old age (60 to 80 years) and then declines (Bonafè et al. 2001; Ukraintseva and Yashin 2003) (Example of age distribution of incidence of colon and rectum cancer for male Swedish population 2000-2009 is available from the Institute for Health Metrics and Evaluation at http://ihmeuw.org/3v13). This nonlinear pattern might be explained by cancer's multistage etiology in which DNA mutations provide stem cells with replicative advantage that promote clonal growth that transitions into in senescence or a malignant neoplasm (Hanahan and Weinberg 2011). The progression of cancer, like CVD, involves immunosenescence and in particular accumulation of senescent cells with age is thought to promote tumor growth (Campisi 2013; Vasto et al. 2009). Therefore, the intrinsic vitality property of a stochastically evolving process provides a first order representation of cancer development. However, the decline in the cancer mortality rate in old age requires further consideration.

Two general explanations for the decline of cancer in old age have been proposed. One involves selective removal of frail individuals that are genetically predisposed to cancer, leaving cancer resistant individuals in old age (Vaupel and Yashin 1986). This mechanism assumes genetic heterogeneity in the inflammation response in which individuals with a weaker response to inflammations are presumably more resistant to cancer (Vasto et al. 2009). However, this mechanism does not easily explain strong declines in cancer incidence in old age. Alternatively, a reduced inflammation response could also result from remodeling of the immune system without invoking population heterogeneity (Bonafè et al. 2001; Ukraintseva and Yashin 2003). The decline in cancer incidence may also involve telomeres through a protective effect of telomere attrition on senescence (Blackburn et al. 2015; Collado et al. 2007), which could inhibit clonal growth. This second mechanism could explain a reduction

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of cancer in old age. However, these mechanisms are not mutually exclusive and the distal component of cancer is likely to involve greater complexity than what is captured by the current two-process vitality model.

In any case, cancer does not fit into a challenge paradigm of extrinsic mortality because the mutations that initiate the clonal growth and metastasis can result from intrinsic or extrinsic challenges (Tomasetti and Vogelstein 2015; Wu et al. 2016). Additionally, the latency between an initial mutation and mortality can span years, which precludes characterizing a specific challenge frequency or magnitude for the process. The proximal causes of cancer deaths are more characteristic of the boundary passage process underlying intrinsic mortality. For example, exhaustion of survival capacity is readily represented by cachexia, a metabolic wasting process with extreme weight loss that is the immediate cause of 20% of cancer deaths (Argiles et al. 2014). Because of the boundary passage nature of the proximal mortality component of cancer and the indeterminacy of the source of cancer initiation we suggest that the vitality model captures cancers as intrinsic mortality. However, it is likely that the intrinsic mortality component of the model also is driven in part by CVD-like diseases.

MODEL

Equations

The two-process model has a foundation in the classification of extrinsic mortality from acute infections and accidents and intrinsic mortality from the remaining COD (Carnes et al. 1996). However, in focusing on processes the model provides a more generalized classification that pairs different distal and proximal components of mortality. For extrinsic mortality, the distal component is represented by age-declining deterministic vitality and the proximal component is represented by random extrinsic challenges. For intrinsic mortality, the distal component is represented by age-declining stochastic vitality and the proximal component is represented by boundary passage (Li and Anderson 2013), which can also be viewed as intrinsic challenges. To this base model we include juvenile mortality with a distal component represented by age-increasing juvenile vitality and a proximal component represented by juvenile extrinsic challenges. Assuming challenges to the respective vitalities do not affect the distribution of the other vitalities then the mortality rates are independent and the total mortality rate for each distal/proximal pairing is

$$\mu(x) = \mu_{a,i}(x) + \mu_{a,e}(x) + \mu_{j,e}(x) \tag{1}$$

where subscript *a,i* denotes the adult intrinsic process while *a,e* and *j,e* denote the adult and juvenile extrinsic processes respectively. The interactions of vitalities and challenges are depicted in figure 1 and described below.

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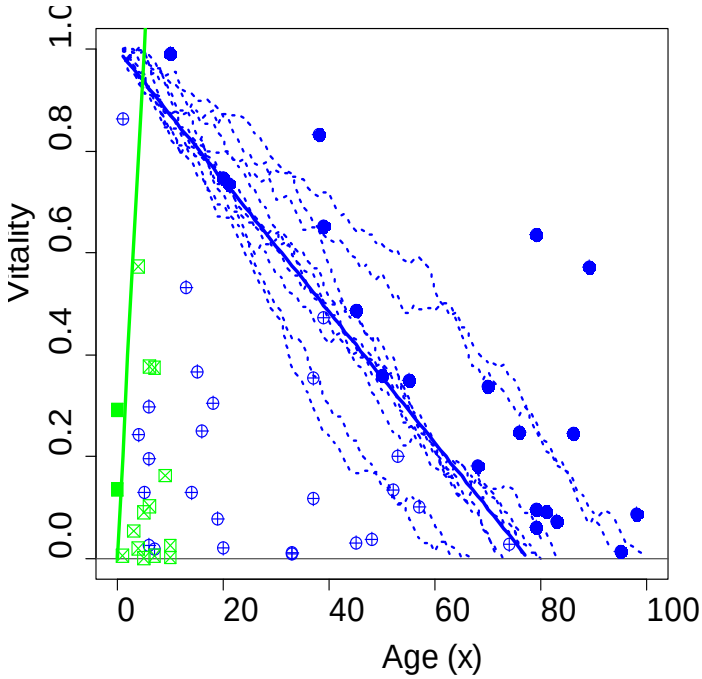

Fig. 1 Depiction of extrinsic and intrinsic mortality processes for equation (5). The green and blue lines represent population-level measures of juvenile and adult vitality respectively where from birth juvenile vitality increases from zero and adult vitality decreases from one. Green squares and blue circles denote juvenile and adult vitality extrinsic challenges. Filled symbols denote juvenile and adult extrinsic deaths in which the challenges exceed juvenile and adult population-level vitalities. Correspondingly, unfilled symbols represent challenges not exceeding the reference vitalities. Adult intrinsic mortality is represented by individual stochastic vitality paths intersecting the zero boundary which we denote an intrinsic challenge. The figure was generated using r = 0.0129, s = 0.0126, λ = 0.045, β = 0.40, γ = 0.15 and α = 1 corresponding to the fit to period data for Swedish females in 1900

Adult intrinsic mortality

Adult intrinsic mortality is generated by boundary passage of a Wiener process (Anderson 2000; Li and Anderson 2013; Weitz and Fraser 2001) as $dv/dx = -r + s\varepsilon_x$ where r is the mean rate of loss of vitality, s is the stochastic intensity of the loss rate and ε_x is a white noise process. We view vitality as a measure of immune system capacity. The rate term r is an index of the rate of development of immunosenescence and s is an index of the population level heterogeneity in the rate. The probability distribution of the first passage time of stochastic vitality trajectories from a unit initial vitality at age x = 0 to the death boundary at v = 0 (figure 1) is given by the inverse Gaussian distribution (Chhikara and Folks 1989),

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$f(x) = \frac{x^{-3/2}}{s\sqrt{2\pi}} \exp\left(-\frac{(1-rx)^2}{2s^2 x}\right)$. Survival from adult intrinsic mortality only, is $l_i(x) = 1 - \int_0^x f(x)dx$ and the adult intrinsic mortality rate is

$$\mu_{a,i}(x) = f(x)/l_i(x). \tag{2}$$

Adult extrinsic mortality

Adult extrinsic mortality, following (Li and Anderson 2013; Strehler and Mildvan 1960), is generated by environmental challenges to adult vitality. Challenge frequency has a Poisson distribution with mean λ. The challenge magnitude z has an exponential distribution $\varphi(z) = 1 - \mathrm{e}^{-z/\beta}$ with a mean β. The conditional extrinsic mortality rate is $m_e\left(x \mid v = v(x)\right) = \lambda \Pr\left[Z > v(x)\right] = \lambda\left(1 - \varphi(v(x))\right) = \lambda e^{-v(x)/\beta}$. Integrating over vitality states, the population-level adult extrinsic mortality rate at age x is $\mu_{a,e}(x) = \int_0^\infty m_e(x \mid v) g(v) dv$ where the age-dependent distribution of vitality $g(v)$ depends on both the loss of vitality through the stochastic process and its modification by the preferential elimination of low-vitality individuals via extrinsic challenges. Because $g(v)$ has no closed form, age dependent vitality is approximated $v(x) = 1 - rx$ giving the adult extrinsic mortality rate (Li and Anderson 2013)

$$\mu_{a,e}(x) = \lambda e^{-(1-rx)/\beta}. \tag{3}$$

Note in equation (3) mortality results from challenges to a linear approximation of the age-declining stochastic vitality distribution. The extrinsic mortality rate is equivalent to the Strehler and Mildvan (1960) interpretation of the Gompertz mortality model (Gompertz 1825) $\mu_{a,e} = a\exp(-bx)$ such that the Gompertz coefficients are related to the extrinsic mortality coefficients as $a = \lambda e^{-1/\beta}$ and $b = -r/\beta$.

Juvenile extrinsic mortality

Juvenile extrinsic mortality is generated by juvenile challenges to a deterministically increasing juvenile vitality. The development follows that of equation (3) except at age $x = 0$ juvenile vitality is zero and increases as the immune system develops giving $v'(x) = r'x$, where the prime designates juvenile parameters equivalent to the adult parameters. The juvenile extrinsic mortality rate from extrinsic challenges is then

$$\mu_{j,e}(x) = \gamma e^{-xr'/\beta'} = \gamma e^{-x/\alpha} \tag{4}$$

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where γ is a base juvenile mortality rate and $\alpha = \beta'/r'$ characterizes the duration of the juvenile period in which mortality is associated with the developing immune system.

Total mortality

The total mortality rate combines equations (2-4) into equation (1) giving

$$\mu(x) = \frac{x^{-3/2} e^{(1-rx)^2/2s^2 x}}{s\left(\Phi\left(\frac{1-rx}{s\sqrt{x}}\right) - e^{2r/s^2}\Phi\left(-\frac{1+rx}{s\sqrt{x}}\right)\right)} + \lambda e^{-(1-rx)/\beta} + \gamma e^{-x/\alpha} \tag{5}$$

where Φ is the cumulative standard normal distribution $\Phi(x) = \left(1/\sqrt{2\pi}\right)\int_{-\infty}^{x} \exp\left(-t^2/2\right)dt$.

Equation 5 parameters are estimated by fitting survivorship curves or mortality data with a maximum-likelihood fitting routine (Salinger et al. 2003). A family of vitality models in R code is available at CRAN.R-project.org/package=vitality. Equation (5) is fit with the package function vitality.6p.

Model properties

The model partitions three types of mortality, which are defined by their distal and proximal components. However, there is no absolute definition of the partitions, nor one-to-one relationships with COD. Thus, to address these indeterminacies sections below briefly discuss the properties of intrinsic and extrinsic mortalities and their hypothesized relationships to COD and physiological processes. The third section discusses the issue of resolving proximal components of mortality.

Intrinsic mortality

For intrinsic mortality, the distal component represents the stochastic loss of immune system capacity through immunosenescence and the proximal component represents the loss of immune system function by passage of vitality into the zero boundary. Cancer is largely captured as intrinsic mortality because the endpoint is typically a wasting process, e.g. cachexia, which is readily represented by exhaustion of vitality. Additionally, the patterns of log mortality rate versus age are similar for cancer and intrinsic mortality, i.e. for both, the increase of mortality rate slows down with age. The model generates this pattern by the removal of lower vitality (cancer susceptible) individuals at earlier ages leaving the higher vitality (cancer resistant) individuals in older ages. Mortality associated with CVD may also be represented as intrinsic mortality under challenge masking conditions, which are discussed below.

Extrinsic mortality

For adult extrinsic mortality, the distal component represents the mean rate of decline of immune system capacity through immunosenescence and the proximal component represents extrinsic challenges to the system's capacity. For juvenile extrinsic mortality, distal vitality

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represents a linearly increasing development of the immune system in early life and the proximal component represents the extrinsic challenges to the immune system. The increase of juvenile vitality has no effect on the decrease in adult vitality, but for adults, extrinsic and intrinsic mortalities are linked since both depend on the mean rate of decline of the adult immune system.

Challenge masking

For adult challenges, the description based on β and λ does not fully capture the distribution of challenges of different magnitudes and frequencies, as is the case with ID and CVD challenges. ID challenges tend to be strong and infrequent, e.g. typhoid epidemic, while CVD triggers are weak and frequent, e.g. physical exertion. While both types co-occur, the model estimates the properties of high magnitude challenges when their frequency is above some threshold level and when it drops below the threshold the model estimates the properties of the competing low magnitude challenges (Li and Anderson 2013). We denote this property "challenge masking" in which strong challenges mask the effect of weaker ones resulting in the weaker challenges being represented as vitality boundary passage. Functionally, weak challenges (e.g. CVD triggers) in the presence of strong challenges (e.g. ID events) can be shifted to the intrinsic mortality category but in the absence of the stronger challenges they contribute mainly to the extrinsic mortality category. In addition, unmasking of weaker challenges also involves an actual decline in the extrinsic mortality rate because ID challenges are removed. Ultimately, the clarity of the intrinsic and extrinsic mortality partition depends on properties of the challenges. An important point is that COD categories included in the intrinsic mortality can depend on the extrinsic challenges, which may change during an epidemiological transition.

RESULTS

Mortality rate patterns with age

Figure 2, showing patterns of the three mortality processes for Swedish period mortality data[1], illustrates the changes in processes underlying the doubling of life expectancy (~40 to ~80 years) between the 19th and 20th centuries (Sundin and Willner 2007). This life span doubling was driven by reductions in juvenile mortality and adult extrinsic mortality for ages < 70 yrs. However, for ages > 70 extrinsic mortality increased while the intrinsic mortality rate decreased. This cross-century change can be attributed to two processes. First, the ID (high magnitude/low frequency) challenges diminished, which reduced juvenile and adult extrinsic mortalities. Second, the reduction of ID challenge frequency unmasked the CVD challenges such that the model shifted CVD-type mortalities from intrinsic to extrinsic categories. Thus, the intrinsic mortality rate decline across the centuries reflects a real decline in ID-type

[1] *Human Mortality Database*. University of California, Berkeley (USAUN), and Max Planck Institute for Demographic Research (Germany). Data downloaded 01/11/2014 from www.mortality.org.

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mortality plus an apparent decline resulting from a shift of CVD-type mortalities from intrinsic to extrinsic categories. The dominance of extrinsic mortality in old age after the epidemiological transition comports with CVD now being the leading COD. Correspondingly cancer, which the model associates with intrinsic mortality, is the second leading COD (Heron 2015). The decline in childhood mortality over the periods can be explained by both the reduction in childhood disease challenges and an increase in the rate of immune system development, plausibly related to increased nutrition in the 20th century (Köhler 1991). The current model does not include young adult challenges, which is evident by the rise of the mortality rate above the extrinsic mortality line between ages 10 and 25 years (figure 2).

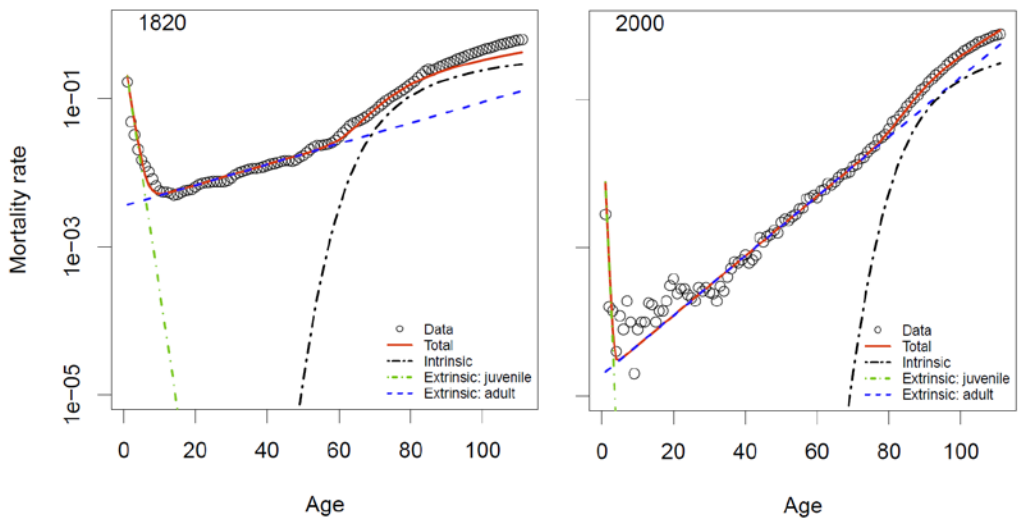

Fig. 2 Period mortality rate components vs. age for Swedish female period data for 1820 and 2000. Data depicted by circles. Modeled total mortality rate is depicted by red lines. Green, dark blue and light blue lines depict mortality rate components adult intrinsic (μ_i), $\mu_{e,a}$, and $\mu_{e,c}$ respectively. Fitted parameters are $r = 0.0129$, $s = 0.0126$, $\lambda = 0.045$, $\beta = 0.400$, $\gamma = 0.2033$, $\alpha = 0.75$ for year 1820 and $r = 0.0107$, $s = 0.0077$, $\lambda = 0.123$, $\beta = 0.115$, $\gamma = 0.0076$, $\alpha = 2.56$ for year 2000

Juvenile extrinsic mortality

The juvenile extrinsic mortality rate, characterized by straight lines in the log mortality rate graph (figure 3*a*), clearly shows two clusters. One cluster (red-green lines, 1751-1905) has a shallow slope with age and the other cluster (purple lines, 1960-2010) has a steeper slope. The epidemiological transition (1905-1960) is evident as a fan of blue lines between the two clusters. The change in the juvenile extrinsic mortality rate exhibits a progressive decline in both the initial rate γ, characterized by line intercepts at age 0, and the duration of juvenile mortality α, characterized by line slopes. The parameter γ reflects both neonatal mortality and the frequency of challenges experienced by juveniles. The cross over age, at which the juvenile and adult extrinsic rates are equal, is depicted by circles passing through each respective line. In the early period (red-green cluster) the crossover age varies from ~ 5 to 7

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years of age, mostly as a result of changes in line slopes, which are expressed by α. We suggest this variability and trend in the crossover age was driven by a series of famines superimposed on a gradual improvement in the nutrition status of children. This is elaborated below in discussion of figure 4*e*. The further reduction of the crossover age and decline in crossover age mortality rate is driven by the reduction in the adult extrinsic mortality rate as characterized by *r* (figure 4*e*).

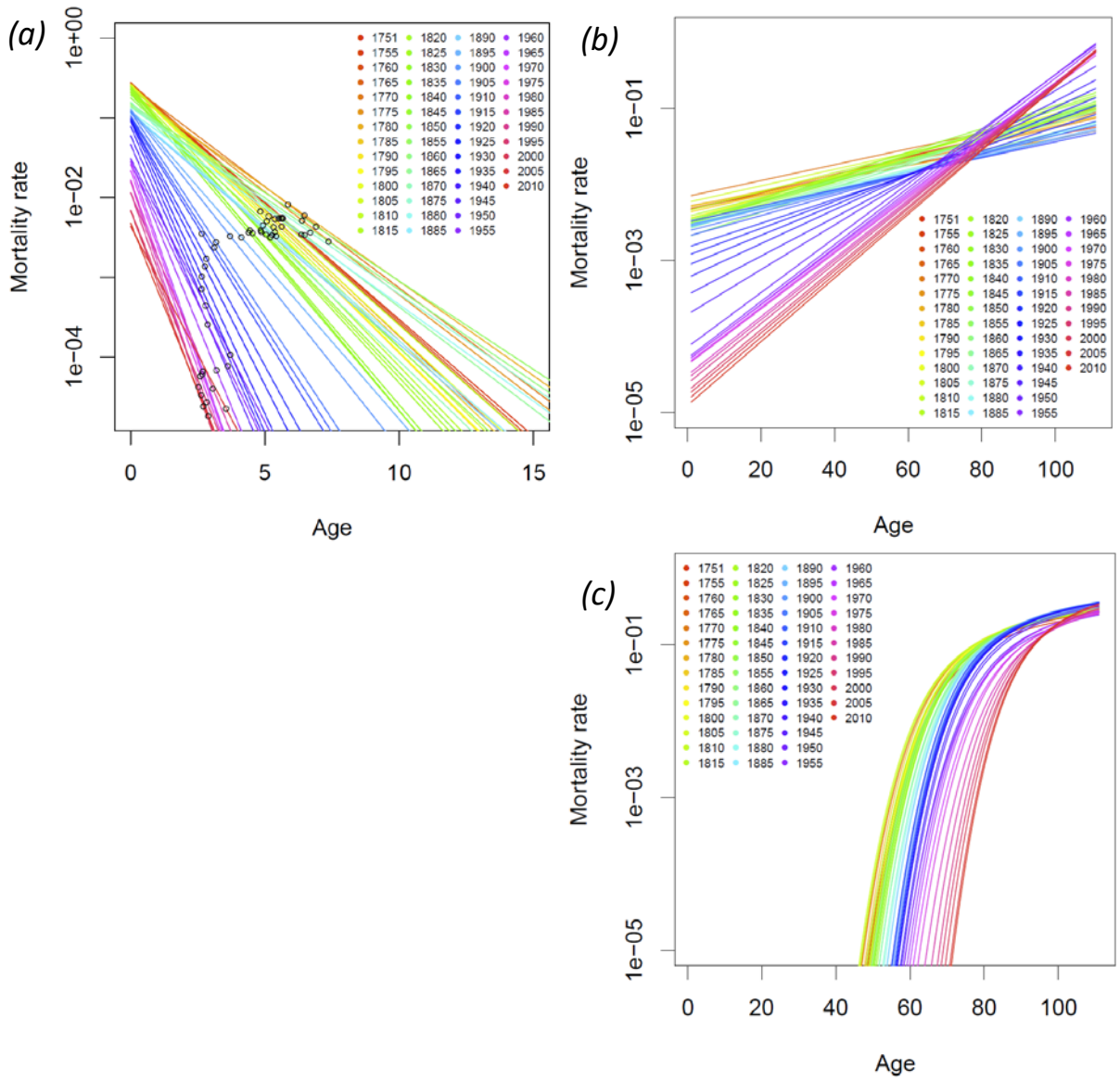

Fig. 3 Lines depict of mortality rate components (year^{-1}) in equation 5 fit to Swedish female period data grouped in 5-year increments (1751-2010). In general, for each graph the mortality rate components decline for increasing 5-year intervals: (*a*) Juvenile extrinsic mortality rate. Circles indicate cross over ages where juvenile and adult extrinsic mortality rates are equal. (*b*) Adult extrinsic mortality rate. (*c*) Adult intrinsic mortality rate.

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Adult extrinsic mortality

The adult extrinsic mortality rate lines (figure 3*b*) cluster in the same manner as the juvenile lines (figure 3*a*). Within each cluster the lines progressively, and uniformly, shift downward as a result of the gradual all-age reduction in the extrinsic mortality rate over years. The two clusters intersect at approximately age 75 years, indicating that in this interval the estimated extrinsic mortality was approximately constant across time. Thus, for ages below 75 years, the extrinsic mortality rate declined over time due to a reduction of strong ID challenges, while above 75 years the rate increased because of the corresponding unmasking of the low magnitude CVD-type challenges. In the red-green cluster, extrinsic mortality was driven mainly by ID challenges, which occurred randomly over the life span, thus the rate of mortality from ID challenges was similar for young and old individuals resulting in a shallow slope in the cluster. In contrast, the purple cluster extrinsic mortality was dominated by low magnitude challenges, which occurred later in life, resulting in a steeper slope for the cluster and a strong age dependence in extrinsic mortality.

Adult intrinsic mortality

The pattern of intrinsic mortality completes the picture of longitudinal changes (figure 3*c*). Notably, intrinsic mortality in old age (> 90 years) changed little over the years suggesting the rate of mortality from cancer in very old age has changed little over time. However, the longitudinal changes in intrinsic mortality are quite significant for middle and early old age. For example, at age 80 the intrinsic mortality rate was ~0.1 in year 1750 and 0.001 in year 2010; a two order of magnitude decline in intrinsic mortality. This decline is not the result of the challenge masking effect since essentially the magnitude of decline occurred within the red cluster (years 1960-2010) in which the extrinsic challenge properties had stabilized. The cause of this decline reflects the cumulative changes over the life span of the individuals, as expressed by *r*, and likely reflects improved nutrition as well as the reduction of exposure to illness through better health programs and vaccinations against infectious diseases.

Vitality parameter longitudinal patterns

Figure 4 depicts the longitudinal patterns of the vitality model parameters for male and female Swedish populations over two centuries. Besides a general improvement in conditions promoting a doubling of longevity over this period of time, the parameters reveal the complexity in the changes that occurred over decades as well as the complexity of the epidemiological transition. Because of the effect of challenge masking involved with the epidemiological transition we discuss the periods before and after the transition separately.

Before mid-20th century

Before the mid-20th century, adult extrinsic mortality declined slowly and erratically (figure 3*b*) as a result of a slow steady decline in the rate of loss of vitality (figure 4*a*) and variability in the challenge magnitude and frequency (figure 4*c* and 4*d*). The gradual decline in *r* in the 19th century (figure 4*a*) corresponds with a significant increase in agricultural production beginning 1790 (Olsson and Svensson 2010), which was driven by the replacement of small farms with large capitalistic farms (Möller 1990). The link between grain production and *r* is

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supported by an observed correlation between the price of rye and the mortality rate over the first half of the 19th century. A 20% increase in grain price corresponded with a 5-6% increase in mortality the next year (Dribe et al. 2012). Because both food availability and its price would affect the level of nutrition (Schaible and Kaufmann 2007), we suggest the pattern of *r* over time reflects the effects of nutrition on the rate of immunosenescence, i.e. higher values of *r* indicate faster rates of immunosenescence.

The vitality rate variability, *s*, was high in the 18th century and then declined over the 19th century (figure 4*b*). This term characterizes the degree of rectangularization in the survival curve, i.e. the steepening of slope of the survival curve about the mean age of life expectancy (Li and Anderson 2009). It also quantifies the heterogeneity in the intrinsic mortality rate of the population. The high levels of *s* in the 18th and early19th century correspond with the differential in mortality between the rural and urban populations (Edvinsson and Lindkvist 2011; Schumann et al. 2013). Nutrition levels were higher and infection levels were lower in the rural environment. Also early in the 19th century mortality rates were lower in the higher social economic groups than in the lower groups (Bengtsson and Dribe 2011). The differential in mortality by both measures declined steadily through the 19th century and into the first part of the 20th century (Bengtsson and Dribe 2011). Thus, we suggest *s*, is a quantitative measure of the effects of heterogeneity in population nutrition on mortality

Noteworthy, in figure 4*c* the frequency of infectious disease and physical injury challenges, λ, did not significantly change through the 18th and 19th centuries for females. However, the challenge frequency increased significantly for males in the first half of the 19th century. This peak in λ corresponds with excessive male mortality between 1820-1850, which was postulated to be related to increased alcohol consumption by males (Sundin and Willner 2007). Also, the male versus female differences in challenge frequency (figure 4*c*) comport with gender-linked risk taking behavior, which was about 20% lower in females than in males (Byrnes et al. 1999). Challenge magnitude (figure 4*d*) exhibited distinct spikes for the years 1808 and 1918, which correspond with disease during the Finnish war (Mielke and Pitkänen 1989) and the influenza pandemic (Sundin and Willner 2007) respectively, suggesting that β tracks the virulence of environmental challenges. This signal in β corresponds with the effects of pandemics to temporarily shift mortality to younger age groups (Reichert et al. 2012), which the model then characterizes as an increase in extrinsic challenges. Finally, the higher magnitude β in females comports with the allocation of resources to males over females (Klasen 1998) in the 18th and 19th centuries. Thus, the extrinsic challenge parameters λ and β quantify notable environmental- and behavioral-associated changes in health.

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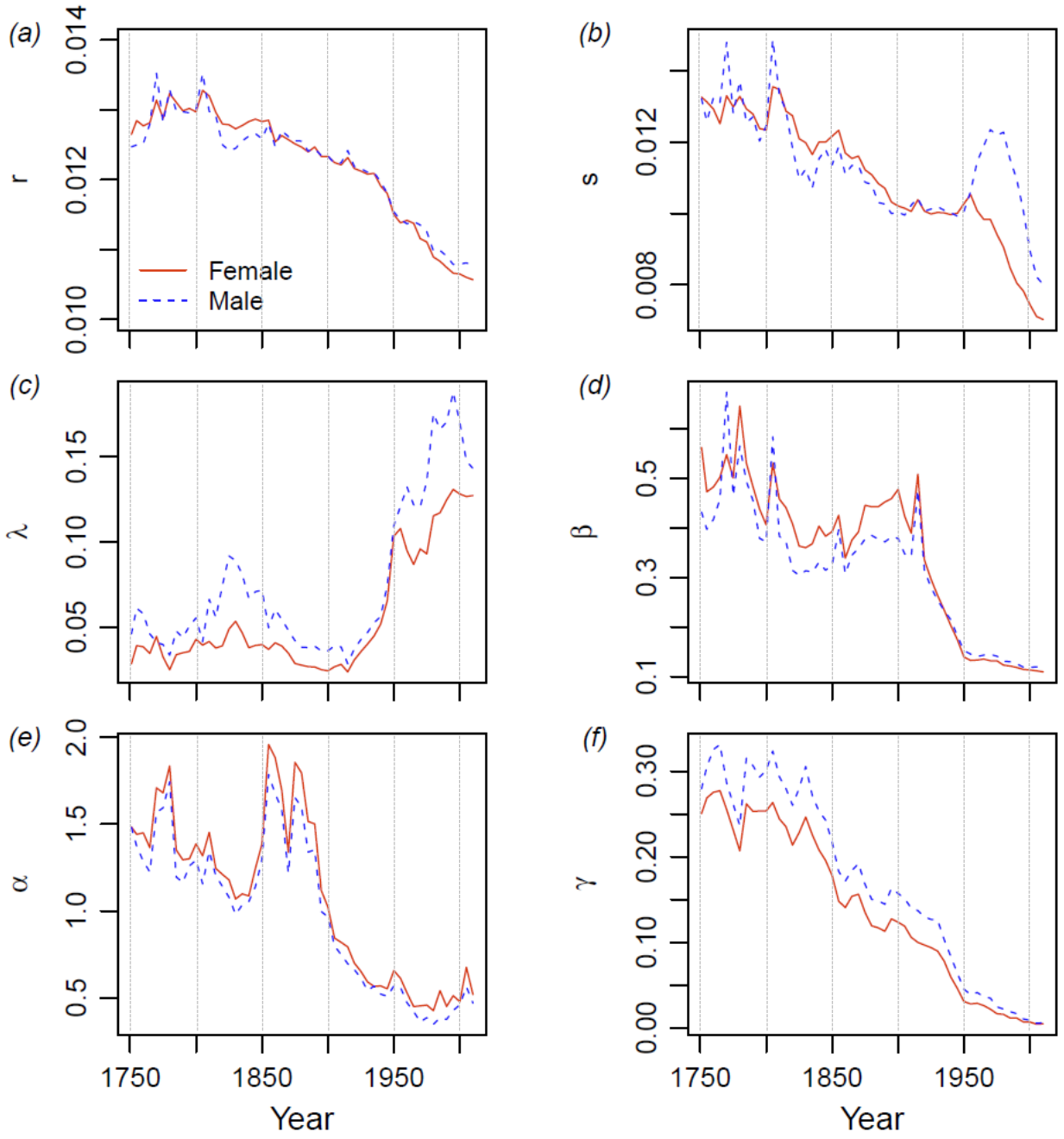

Fig. 4 Longitudinal patterns of vitality parameters for the Swedish population (1750-2010). Male and female patterns are depicted as dashed (blue) and solid (red) lines separately. (*a*) vitality loss rate (year^{-1}), (*b*) variation of vitality loss rate (year$^{-1/2}$), (*c*) average adult extrinsic challenge frequency (year^{-1}), (*d*) average adult extrinsic challenge intensity, (*e*) half-life of juvenile mortality (year), (*f*) base juvenile mortality rate (year^{-1}).

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The index of juvenile mortality duration, α, exhibited peaks (figure 4*e*) corresponding with famines in 1772-1773 and ~1860-1870 (Sundin and Willner 2007). Note that starvation represents only a small fraction of the mortality associated with famine. The majority of deaths are due to infectious diseases associated with malnutrition (Sundin and Willner 2007). Thus, we suggest that because $\alpha = \beta'/r'$ it follows that the peaks in α were the result of reduced food supply that decreased the rate of immune system development, i.e. reduced r'. A series of nine cholera epidemics between 1834 and 1874 also may have contributed to the elevated α over the same period through the effect of cholera on the juvenile challenge magnitude, β'. The steady decline in the initial mortality rate γ (figure 4*f*) through the mid-20th century does not correspond with specific health events. Noteworthy, the initial mortality rate was uniformly higher in boys than girls, a feature also observed in other populations (Sundin and Willner 2007).

After mid-20th century

The mid-20th century epidemiological transition is evident by a sharp decline in the vitality loss rate, *r*, in males and females about ~1945 (figure 4*a*). About 1950 the trend in female *s* exhibited a decline while the male trend increased, peaking ~1975 (figure 4*b*). The decline in female *s* is potentially a continuation of the postulated trend in decreasing heterogeneity in the rate of immunosenescence in the female population. The rise and peak in *s* for males can be explained by increasing heterogeneity in their rate of immunosenescence due to a divergence in the social economic pattern of smoking. About 1950 the male smoking rate started to decline in the professional/managerial group but the decline in the agricultural/industrial group did not begin until the end of the century (Diderichsen and Hallqvist 1997). Thus, the peak in *s* in ~1975 can be explained by the lag in the reduction of smoking between the two groups. The model does not identify the COD associated with the peak in *s*. However, in the period 1965-80 the leading COD in the agricultural/industrial group was CVD (Diderichsen and Hallqvist 1997). Because *s* only occurs in the intrinsic mortality equation and its level is most influenced by the curvature of the mortality rate in old age, the peak was driven by differences in the mortality rates of the two social economic groups in old age.

The rapid decline in challenge magnitude from 1920 to 1950 (figure 4*d*) is coincident with measures to control tuberculosis, the discovery of streptomycin (Daniel 2006) and development of a range of antibiotics for other infectious diseases. The slower decline in challenge magnitude post-1950 can be explained by two factors. Firstly, the extrinsic mortality in this period was driven by CVD-type mortalities, which were flat over the period (Vangen-Lønne et al. 2015). Secondly, CVD mortality is triggered by every-day physical exercise which has not changed significantly over the last half century. Thus, the flat pattern of β reflects the low magnitude of proximal triggers of CVD mortalities. Finally, in the 21st century extrinsic mortality exceeds intrinsic mortality, which comports with the COD data in which in the 21st century mortality from degenerative diseases exceeds that from malignant neoplasms (World Health Organization 2010).

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The 20th century decline in α (figure 4*e*) corresponds with improvements in Swedish postnatal care and child nutrition (Köhler 1991). The decline in the initial juvenile mortality rate γ likely reflects improvements in neonatal care in the second half of the century (figure 4*f*).

DISCUSSION

This paper describes a process point-of-view approach to modeling mortality patterns, and outlines a framework for characterizing causes of death in terms of separate processes leading up to and responsible for death. We designate these the distal and proximal components of mortality. The framework has its basis in the Strehler-Mildvan (1960) interpretation of the Gompertz model that characterizes interactions of the proximal and distal components in a mortality event in terms of external challenges exceeding the level of the age-declining vitality. This framework was extended in Li and Anderson (2013) by including a second proximal component, characterized by the passage of vitality into a zero boundary. This expanded model was designated a two-process vitality model to denote the two different forms of mortality: extrinsic mortality induced by challenges to vitality and intrinsic mortality induced by vitality boundary passage.

In this paper we extend the process point of view by seeking candidate biological processes underlying the concept of distal vitality and proximal events. In this task we were immediately confronted with the reality that the framework does not neatly partition mortalities into distinct extrinsic and intrinsic categories. The task then is to select distal and proximal components of mortality that have biological foundations, but which are sufficiently general to explain, at a tractable level of complexity, the historical patterns of mortality, and forecast future patterns of mortality under alternative scenarios of environmental and population health.

For our example, we defined the distal component of mortality in terms of the age-evolving pattern of the immune system. This led immediately to the need for two distal components, one characterizing effects of immune system development in juveniles, and a second characterizing effects of immune system degradation in adults. The model also incorporates the two forms of the proximal components of mortality: extrinsic challenges and vitality boundary passage. This revised framework thus requires a two-component designator of mortality: an identifier of the distal component concatenated to an identifier of the proximal component. Our example generates three forms of mortality defined by distal-proximal pairings: juvenile extrinsic, adult extrinsic and adult intrinsic. The parameters defining the mortalities are respectively (α, γ), (β, λ, r) and (r, s).

The model was applied to Swedish mortality data, and the patterns of fitted model parameters were qualitatively compared to historical patterns of environmental, economic, health and cause of death patterns. The comparison illustrated that, while the model parameters and historical information exhibited clear and biologically meaningful correspondences, the three-category partition of mortality did not have a one-to-one correspondence with causes

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of death. Specifically, prior to the 20th century epidemiological transition, adult extrinsic mortality tracked patterns of infectious disease and adult intrinsic mortality largely tracked degenerative diseases and malignant neoplasms. After the transition and the corresponding reduction of infectious disease, the extrinsic mortality component largely tracked the pattern of degenerative diseases while the intrinsic mortality component captured a mixture of degenerative diseases and malignant neoplasms. We conclude that the partition between the adult components depends on the characteristics of the challenges. We termed this "challenge masking" to reflect the effect of strong challenges (e.g. typhoid) masking the effects of weak challenges (e.g. exercise induced myocardial infarctions). This masking was not unexpected and illustrates that while the model quantitatively partitions mortalities into components, the processes underlying the partition, and in particular specific causes of death, are not easily separated with mortality data alone.

In a practical sense, we view a mortality partition, such as the adult extrinsic/intrinsic partition, as a hypothesis of the contributions of different competing distal and proximal factors shaping cause of death patterns. Validating these hypotheses and further identifying the underlying mechanisms will require independent quantitative and qualitative information. For example, the model prediction of extrinsic mortalities dominating intrinsic mortality in old age (figure 2*b*) is supported by data showing that CVD is the leading cause of death while cancers are the second leading cause. This ordering of causes supports the model inference that CVD are a form of extrinsic mortality while cancers are a form of intrinsic mortality. Furthermore, the model provides a quantitative assessment of the change in significance of CVD and cancer with age and in particular characterizes the reduction of cancer incidence relative to CVD in very old age.

It remains to be determined to what degree the mortality partitions can be better linked to specific causes of disease and underlying biological processes. Some extensions should be relatively straightforward. For example, characterizing excess mortality in young adults with a distribution of challenges representing risk-taking mechanistically fits with theories and observations of the young adult mortality hump. However, partitioning contributions of CVD and cancers to patterns of old age mortality is more problematic. In the current form of the model these processes share a common distal component, the rate of loss of vitality r. However, the etiologies of the two diseases are significantly different and therefore a more precise partition will likely require separate rates of loss of vitality for CVD and forms of cancer. In any case, irrespective of the complexities, the process point of view offers a new approach to reconcile patterns of cause-specific mortalities with patterns of all-cause mortality, a topic under active discussion (Alai et al. 2015; Beard 1971; Foreman et al. 2012; Tuljapurkar 1998).

Lastly, we return to the question of the contribution of the process point of view, which currently makes only a small contribution to population sciences. Our perspective of the value of the process approach in the face of the dominance of the mortality-rate approach (Booth and Tickle 2008) can be illustrated through the debate on the limits of human longevity. Over

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the years, several papers have predicted a plateau in longevity based on largely qualitative assumptions that the gains over the 20th century are unlikely to be repeated with further life-style changes and medical enhancements (Olshansky et al. 2001). The counter argument, that a plateau is not impending, is based on the fact that life expectancy has increased in a linear manner for the past 160 years. Therefore, unforeseen future improvements may very much increase longevity in the 21st century (Oeppen and Vaupel 2002). Neither argument is based on a clear understanding of what processes contributed to the past trends in longevity nor what changes are possible at the cellular level that ultimately determines longevity. It seems clear that merging the sciences that study the cellular mechanisms of aging and mortality with the sciences that project consequences to populations is the next logical step in demography. We suggest this step requires a framework that mathematically links mortality processes to mortality outcomes.

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