Evolution of the Human Lifespan, Past, Present, and Future: Phases in the Evolution of Human Life Expectancy in Relation to the Inflammatory Load[1]

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Introduction

This essay considers environmental and life-style factors in natural selection during the three hundred thousand generations that separate us from a great ape ancestor. Humans have the evolved greatest life expectancy (LE) among the primates (fig. 1). The LE at birth of pre-industrial humans, ca. 30–40 years, is twice that of the four extant great ape species (Finch 2007, 2010a; Finch and Austad 2011). The longer human LE is associated with slower postnatal maturation and with lower mortality as adults than the great apes. While these differences are clearly seated in genetics, recent environmental improvements have further increased LE. Since 1800, during industrialization and economic development, the LE doubled again, reaching 70–85 years in favored populations (Christensen et al. 2009). Not only was survival at early ages enhanced, but the LE at age 70 has also more than doubled (Finch and Crimmins 2005). The recent rapid increases in lifespan within ten generations are consistent with environmental factors, rather than genetic selection. The limited heritability of human lifespans, about 25% in identical twins (Herskind et al. 1996; Finch and Tanzi 1997), also shows the importance of environmental and epigenetic factors in aging processes (Finch and Kirkwood 2000; Kirkwood and Finch 2002; Martin 2011). Infection and inflammation have had recognized roles during the recent increases of LE, which I propose

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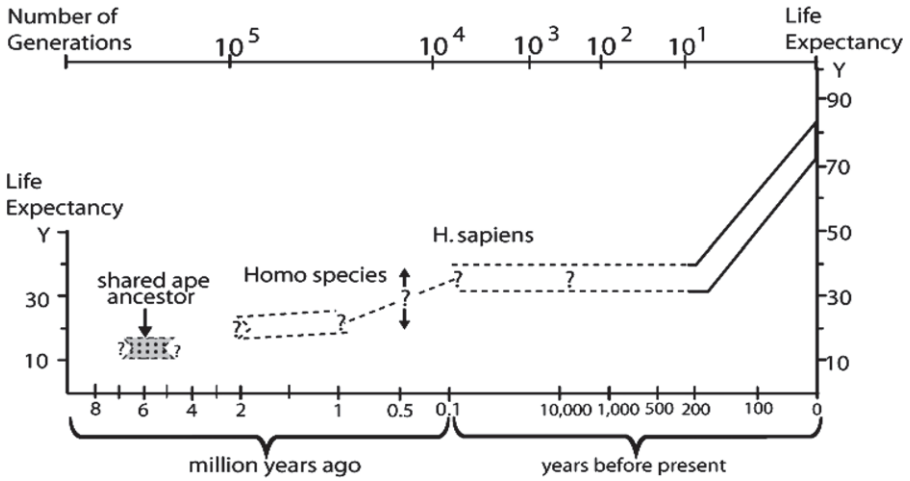

FIGURE 1. Evolution of the human life expectancy (LE) (Finch 2007 adapted from fig. 6.1. Elsevier Press). The LE at birth of the shared great ape ancestor is hypothesized to approximate that of chimpanzees, which are the closest species to humans by DNA sequence data. The LE of chimpanzees at puberty is about 15 years, whereas pre-industrial humans had LE at puberty of about 30 years (Kaplan et al. 2000). Since 1800 during industrialization, LE at birth (Oeppen and Vaupel 2002), as well as at later ages (Finch and Crimmins 2005) has more than doubled. LE estimates for ancestral *Homo* species are hypothesized to be intermediate based on allometric relationships (Finch 2007, p. 375). Ages of adult bones cannot be known accurately after age 30 even in present skeletons (Finch 2010b). The proportion of adults to juveniles does, however, suggest a shift toward greater LE at birth (Caspari 2004; Trinkaus 2011). The few samples in any case cannot give statistically reliable estimates at a population level. The number of generations is estimated at 25 years for humans.

were also important in our evolutionary past. Last, I also consider how global environmental deterioration and emerging climate changes could increase global inflammatory exposure and potentially reverse recent gains in LE.

Mortality Curve Analysis

The huge recent increases in LE are concurrent with the improvements in hygiene, nutrition, and medicine during the nineteenth and twentieth centuries that reduced mortality from infections at all ages. A hypothesis developed with Eileen Crimmins proposes that these reductions in mortality were enabled by a reduced load of chronic inflammation and infection. The load of infection and inflammation is represented by mortality at early ages, which is dominated by infectious causes (Finch and Crimmins 2004, 2005; Crimmins and Finch 2006a; Finch 2007).

Inflammation is closely linked to most chronic diseases of aging, including atherosclerosis and cancer (Finch 2007, 2010a,c; Franceschi 2007; Van Den Biggelaar et al. 2004). Consider two textbook examples: The twentieth-century scourge of tobacco smoking is well understood as causing chronic inflammation with oxidative stress that accelerates vascular aging (carotid thickening) and causes DNA damage and increased cancer. The common gut bacterium *Helicobacter pylori*, once pandemic and now increasingly restricted, increases cancer risk in association with chronic inflammation and DNA damage.

The historical shifts in mortality are graphed as mortality rates by historical cohort, which have a "J-shaped" curve (fig. 2A). Data may be plotted by period, i.e., cross-sectionally, representing all ages present for a given year. Alternatively, tracking a birth cohort across its lifespan reveals additional features of lingering environmental effects. When mortality rates are graphed by cohort, the curves show more distinct trajectories than if plotted by period, with progressive displacement downward across the lifespan during the last two hundred years. The most complete demographic history is from the national data of Sweden since 1750 (Finch and Crimmins 2004; Crimmins and Finch 2006a,b).

Four phases can be resolved in human mortality curves: Mortality Phase 1, decreasing mortality from birth to puberty (0–9 years); Phase 2, basal mortality, which is the lowest during the lifespan (10–40 y); Phase 3, exponentially accelerating mortality (40–80 y); Phase 4, asymptoting mortality (>80 y), which approaches a maximum of 0.5/y after 100. The acceleration of mortality in adults, during the long ascending Phase 3, is described by the Gompertz exponential model:

$$m(x) = A\exp(Gx) \qquad \text{Eq. 1}$$

G is the Gompertz coefficient and A is the intercept (initial mortality rate), usually extrapolated to age 0 (Strehler and Mildvan 1960; Hawkes et al. 2010) or to age at puberty (Finch et al. 1990). However, age 40 is more appropriate for Gompertz modeling, as the age of onset of mortality accelerations in most populations (Beltrán-Sánchez et al., in press).

First I discuss the historical changes in Sweden and other European countries from 1800 as cohort effects, which show direct links of early age mortality to later age mortality (Crimmins and Finch 2006a,b). Specifically, neonatal mortality, which is largely due to infections, co-varies with the birth cohort mortality at age 70 in Sweden, as well as in England, France, and Italy (fig. 3A). These correlations were much weaker for period relationships of mortality of neonates to age 70 (Crimmins and Finch 2006a). Both women and men show these trends (Crimmins and Finch 2006b). In net effect, we hypothesize that aging

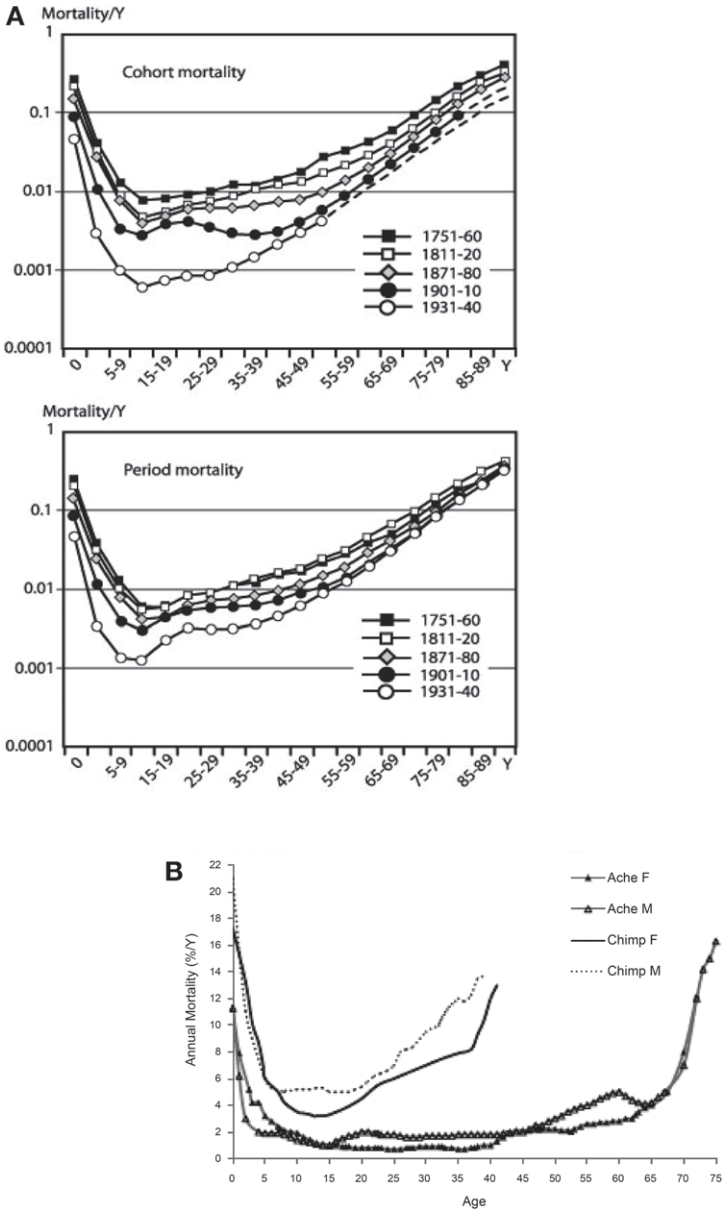

FIGURE 2. A. Swedish mortality rates from household census data, starting before 1750 plotted on a semi-log scale; data from Human Mortality Database (Finch and Crimmins 2004). Finch 2007 fig. 2.7. B. Annual mortality of feral chimpanzee and select hunter-foragers (Kaplan et al. 2000). Note the higher background mortality of chimpanzees aged 10–20 (subadult and adult) than humans living under pre-industrial conditions without modern medicine. The mortality accelerations associated with senescence begin much earlier in chimpanzees than in any human population.

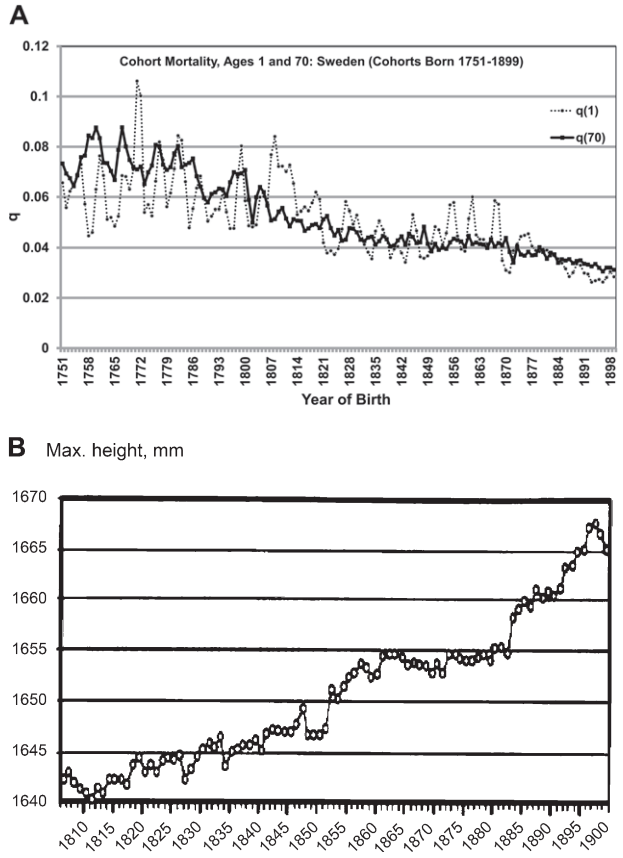

FIGURE 3. Swedish cohorts show links of early infection exposure to adult height and later mortality rates. A. Mortality before age 10 up through 1950 is largely due to infections. It is hypothesized that survivors of high early mortality carried a load of infections and inflammatory burden that was proportional to mortality in their birth cohort (Finch and Crimmins 2004; Crimmins and Finch 2006). The tight linkage between mortality at early and later age (70 years; q1 and q70) is attributed to persistent inflammation and infections that, in specific examples, are known to promote atherosclerosis and other chronic diseases with an inflammatory component (Finch 2007b). B. Adult height reflects growth during childhood, which is known to be attenuated by childhood infections (Finch 2007, pp. 267–69; Crimmins and Finch 2006).

has been slowed in proportion to the reduced exposure to infections in early life. The high mortality rates of early cohorts may be described as "cohort morbidity," which we hypothesize is due to the load of infections and inflammation carried by survivors of early age mortality (Finch and Crimmins 2004; Crimmins and Finch 2006a). Thus, early damage from infections and chronic inflammation persists throughout life even as the environment improves. Although infections are

recognized as the main causes of death across the lifespan in the preindustrial world, cardiovascular conditions have been recorded as important causes of adult mortality in nineteenth-century Sweden (Preston et al. 1972; Preston 1976). Moreover, it is well recognized that the combination of vascular disease with infections increases mortality risk, as observed in recent influenza pandemics (Reyes et al. 2011).

Further analysis shows that the early age mortality (Phase 1) in nine European cohorts 1800–1915 accounts for 80% of variance in the intercept at age 40 (initial mortality rate at the onset of mortality acceleration) and in the Gompertz acceleration constant (eq. 1) (Beltrán-Sánchez, Crimmins, Finch, in press). These historical trends apply to both genders. In essence, women's mortality curves are displaced slightly below mens' across mortality Phases 2 and 3 of adult life.

These findings extend our conclusions on cohort morbidity and later mortality rates at age 70 (fig. 3A) to the Gompertz mortality model. Significantly, the majority of the benefits of lower early mortality occur because of lower mortality at age 40, when mortality accelerates. These findings also extend the inverse relationships between ln *A* and *G* (Strehler and Mildvan 1960), which were derived from 1950 cross-sectional WHO data. Although Yashin et al. (2002) found that the Strehler-Mildvan relationships were "unstable" for Swedish cohorts, we found them valid for a larger data set for the nine European countries.

It may seem paradoxical that healthy modern populations with ever-lengthening LE nonetheless show faster mortality acceleration rates during aging. The major cause of increased LE remains the >90% reduction of background mortality (Phases 1 and 2). The LE would have been even greater if mortality rates had also not accelerated by ca. 50% since 1800. The exact cost to LE of faster mortality acceleration is not yet calculated. The faster mortality accelerations also contribute to the narrowing distribution of ages at death, with shifts in modal age at death (most frequent age class) to later ages. The narrowing distribution is also represented by the decreasing coefficient of variation of the modal age at death in cross-sectional data (Canudas-Romo 2008; Engelman et al. 2010) and is a basis for the "compression of morbidity" at later ages (Fries 1980; Kannisto 2001; Canudas-Romo 2008).

Twentieth-Century Examples

These historical associations are strongly supported by recent examples, which strongly demonstrate influences of the early life environment on adult health. Studies begun in the 1980s by David Barker and colleagues defined the importance of maternal malnutrition and low birth weight to adult risks for diabetes, obesity, and vascular disease

(Barker and Osmund 1986; Barker et al. 1989; Barker et al. 1993; Barker 2007). Prenatal and postnatal developmental influences on adult chronic metabolic and vascular disorders now represent a major field (Godfrey et al. 2010; Case and Paxson 2010; Symonds et al. 2009). Nutrition also has had a major role in the improvements of LE, because greater year-around access to fresh fruit and vegetables has improved resistance to infections. Fogel and Costa (1997) described the complex of nutritional, medical, and hygienic improvements of the nineteenth and twentieth centuries as a "technophysio revolution," which is further documented in an important new monograph, *The Changing Body: Health, Nutrition, and Human Development in the Western World since 1700* (Floud, Fogel, Harris, and Hong 2011). Subsequent advances in the understanding of atherosclerosis, cancer, and obesity have made it clear that the reduction of chronic infections and inflammation during the last 150 years is directly linked to improved LE, because all of the chronic diseases of aging have inflammatory components (Finch 2007, 2010a,c).

Besides maternal metabolism, infections in well-nourished populations also have lasting imprint, as illustrated by the 1918 influenza pandemic. The peak mortality occurred in the fall of 1918 and faded toward seasonal norms by early 1919. In national data across the U.S., the cohort born in the first 3 months of 1919 had deficits of education (Almond 2005; Almond and Mazumder 2006). Furthermore, the men of the 1919 cohort were slightly shorter at enlistment in World War II, as found in collaboration with these authors (Mazumder et al. 2010) (fig. 4A). These developmental effects are concurrent with population exposure to influenza during middle or late pregnancy. Sixty years later, the 1919 birth cohort incurred 25% excess of heart disease, with the strongest effects on those born in the first three months of 1919 (fig. 4B). Our analysis controlled for seasonal effects on heart disease (Doblhammer and Vaupel 2001). However, we could not evaluate effects of birthweight or maternal health histories, for which data are lacking. The exceptional virulence of the H1N1 virus is attributed to severe pneumonias from secondary bacterial infections to which pregnant women were especially vulnerable (Morens et al. 2008; Brundage and Shanks 2008). The general health and nutritional status of the U.S. at that time is considered good, and most recovered from the flu. However, pregnant women were noted to have had more serious illnesses. Indirect effects of stress during pregnancy are the most likely cause, because the H1N1 virus does not directly reach the fetus (Shi et al. 2005). In mouse models, sterile immune activations with poly d(IC) cause alterations of brain development similar to those caused by H1N1 (Shi et al. 2009). Other rodent models causing transient increases of corticosteroids and

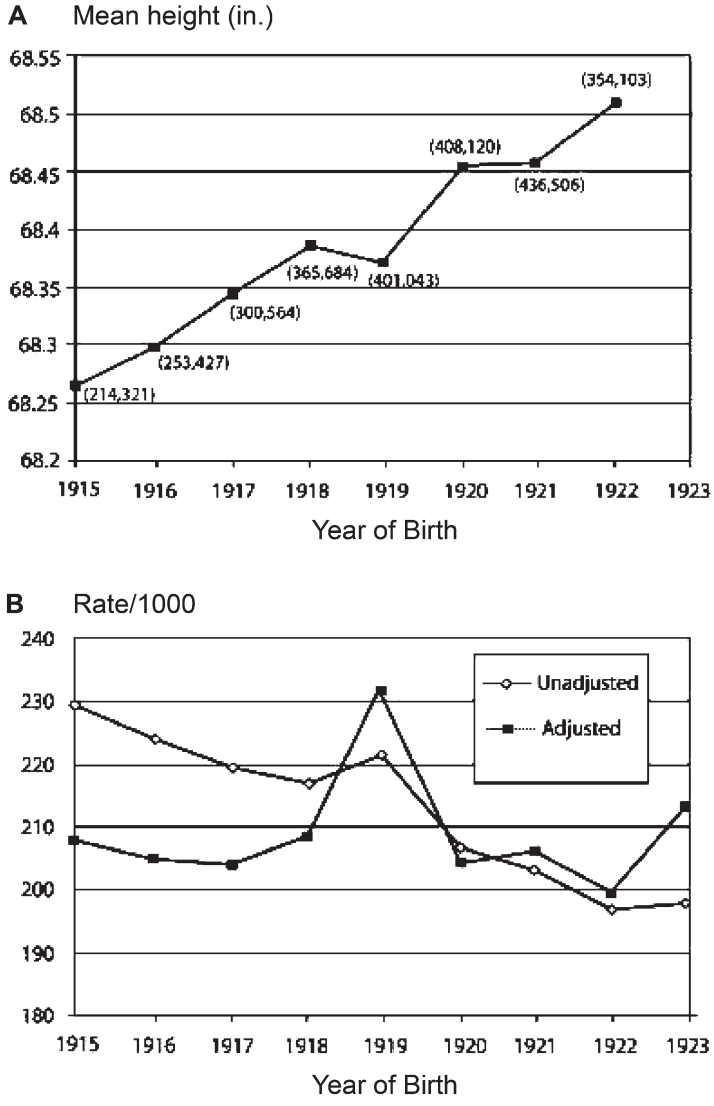

FIGURE 4. The Great Influenza Pandemic of 1918 left lasting imprint on those exposed prenatally, who had slightly impaired growth and 25% excess heart disease after age 60. A. The 1919 U.S. birth cohort was slightly shorter at enlistment of men in World War II. B. This birth cohort also had excess heart disease after age 60. The heart disease associations are strongest in births January–March of 1919, who were exposed to maternal influenza during the second and third trimesters of gestation. Data are adjusted for seasonal effects. No data are available on individual maternal infections or birthweight (Mazumder et al. 2010 *JDOHaD*).

IL-6 during pregnancy show transplacental effects on kidney and hypothalamic functions that predispose to adult hypertension and cardiovascular dysfunctions (Samuelson et al. 2004; Ortiz et al. 2003).

Other examples from the pre-antibiotic era show associations of adult heart disease with early exposure to infections. Childhood rheumatic fever is another classic association of infections with heart disease, in which streptococcus A infections caused endocarditis and valve mitral damage; most died before age 15 from the heart damage, but a few survived to age 40 (Finch 2007, p. 115). In Norwegian adults aged 40–69, mortality from ischemic heart disease was proportionate to the levels of infant mortality in these birth cohorts, 1869–1925 (Forsdahl et al. 1977). Barker's analysis of births in England and Wales 1921–25 also showed strong correlations with infant mortality, infections, and later life morbidity (Finch 2007, pp. 241–43). For example, death from ischemic heart disease at ages 35–74 correlated strongly with neonatal mortality (*r*, 0.68), infections being the majority cause (Barker and Osmond 1986). I suggest broadening the concept of "developmental origins" to include three groups of factors: nutritional deficits, chronic stress from socio-economic factors, and direct and indirect damage from infections (fig. 5).

Adult chronic infections can also accelerate vascular disease. A major contemporary example is HIV/AIDS, in which successful antiretroviral therapy (HAART) has increased life expectancy. However, survivors are incurring higher levels of coronary disease and stroke relative to the non-infected age group (Rockstroh et al. 2010; Voelker 2011) and non-AIDS-defining cancers (Shiels et al. 2011). These links between infections and vascular disease suggest that the highly infectious environment before 1900 would also have promoted vascular disease.

Modern populations present severe obstacles to studying associations of inflammation and cardiovascular disease, because many modern medications interact with inflammatory system pathways, e.g.,

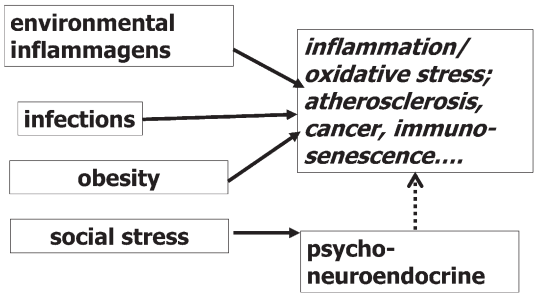

FIGURE 5. Schema: Original

aspirin and statins. However, there are important opportunities to study these processes in a few remaining non-acculturated hunter-gatherers who in the later twentieth century had low life expectancies and limited access to modern medications (Gurven and Kaplan 2007). Crimmins and I are collaborating with anthropologists Michael Gurven and Hilliard Kaplan, who study the Tsimane. This hunter-forager-farmer group from the Bolivian Amazon (population ca. 7,000) has had short lifespans with LE at birth of 42 years, which approximates eighteenth-century Sweden and other pre-industrial European populations. Early mortality is high in association with rampant infections: 60% carry at least one parasite (Vasunilashorn et al. 2010). Blood C-reactive protein (CRP) levels (fig. 6A) and the total white blood cell counts (fig. 6B) are high at all ages, e.g., 25% had CRP >10 mg/dl, consistent with acute or chronic infections (Gurven et al. 2008). The most prevalent Tsimane alleles for CRP and IL-6 are considered pro-inflammatory in European populations, which may contribute to the elevated CRP and other inflammatory markers (Vasunilashorn et al. 2011).

Given the many associations of inflammation with vascular disease, we anticipated its high prevalence. However, in sizable population samples of adults, blood cholesterol (total-C; fig. 6D) and blood pressure (fig. 6E) were below U.S. norms (Vasunilashorn et al. 2010), e.g., only 3% over 40 y had elevated blood pressure, and none had indications of peripheral arterial disease by the ankle-brachial index (ABI) (Gurven et al. 2009). The low body mass index (average BMI of ca. 23; fig. 6C) is below U.S. norms for the corresponding ages, consistent with the Tsimane meager average daily diet with low levels of saturated fat (Reyes-Garcia et al. 2008). Ongoing studies of heart function indicate a low incidence of ischemic artery disease, also consistent with the low levels of blood cholesterol and blood pressure. The Tsimane are undergoing rapid acculturation, which brings access to modern medicine through Bolivian government clinics, but also access to diets richer in unsaturated fats. The Tsimane are giving a unique and fleeting opportunity to study relationships of infection, inflammation, and diet to cardiovascular disease and other aspects of aging in modern industrial populations.

The paleopathology in some ancient civilizations is being approached in a limited way through the study of mummies. Ancient Egyptians incurred advanced atherosclerosis, as shown in a radiological study of mummies of the noble classes from the Old and New Kingdoms (Allam et al. 2011; Finch 2011). About half (20/44) the adult mummies had calcification of coronary and other arteries (average estimated age 45), and these were about 10 years older than mummies without detectable calcification. The ages of these or other ancient skeletal remains cannot be known much closer than within a decade, based on the intrinsic

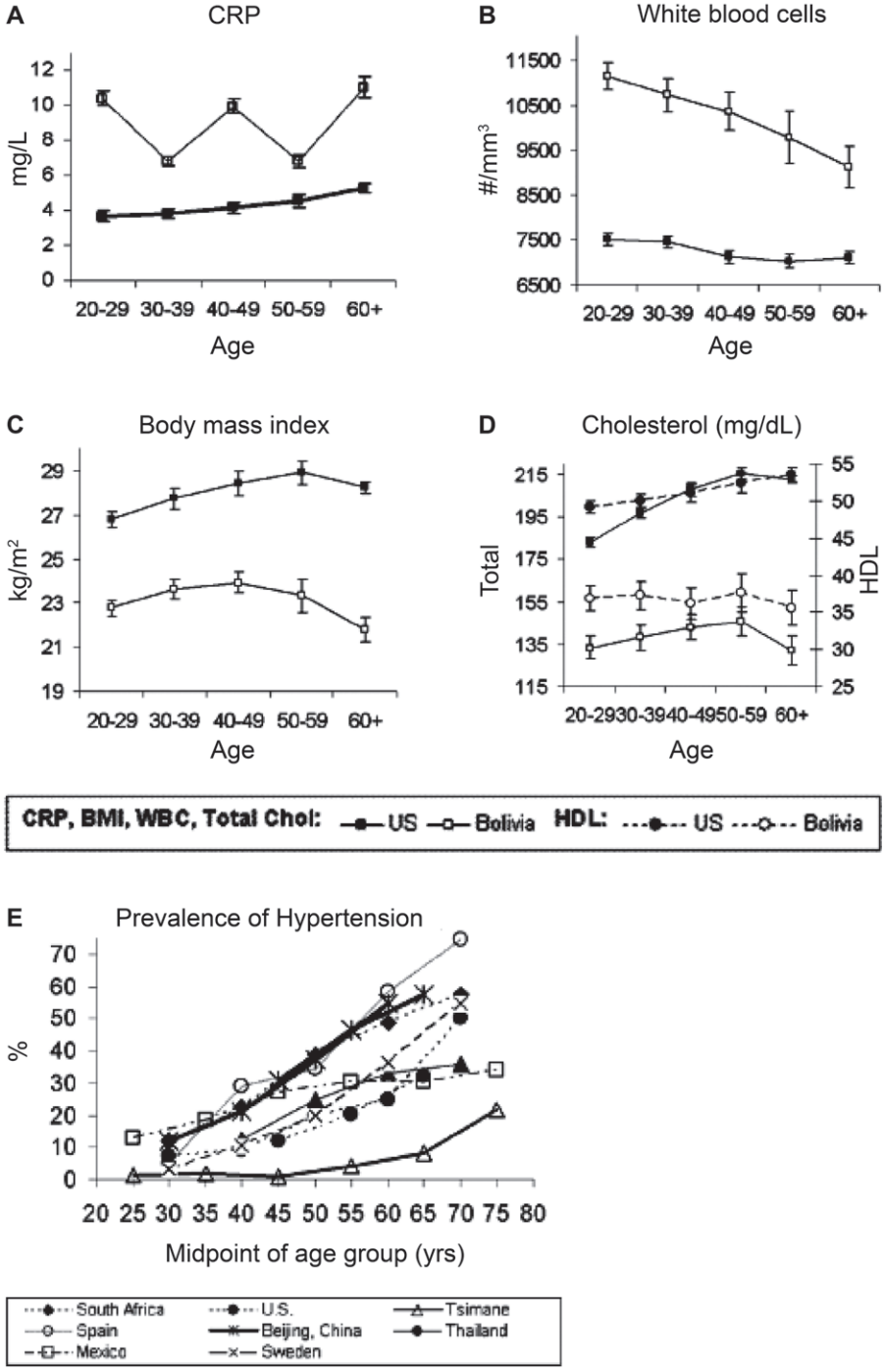

FIGURE 6. Tsimane (Gurven et al. 2009 *PLoS One*)

uncertainties of bone age markers (Finch 2010b). These findings extend the pioneering studies of mummies by Marc Ruffer of a century ago. He described macroscopically visible atherosclerotic plaques in 16/24 adult mummies (Ruffer 1911; Magee 1998). Although there are no ancient records of the daily diet, the noble class had access to foods rich in saturated fats (fattened fowl and cattle), as depicted on tomb paintings (David et al. 2010). Several statues of noblemen portray obesity—that of Hemiunu from the Old Kingdom shows conspicuous pectoral fat (Roemer- und Pelizaeus-Museum). We do know that ancient Egyptian nobles, like the Tsimane, carried tuberculosis and other pathogenic bacteria (Donoghue et al. 2010; Zink et al. 2000), and tapeworms (*Taenia*) and other parasitic worms (Bruschi et al. 2006; David 1979; Le Bailly et al. 2010). The arterial calcification in Egyptian mummies is anticipated by the early Bronze Age "Tyrolean iceman," who died at about 45 years and had remained frozen since ca. 3300 BCE. Utze, as he is called, shows arterial calcification in both carotids (Murphy et al. 2003).

While there is no doubt that infections were the major cause of death in ancient times as in recent pre-industrial populations, the combination of vascular disease with infections nonetheless increases mortality risk, as noted above (Reyes et al. 2011). In anticipating further data on mummies, several caveats must be kept in mind: it is difficult to estimate the bone age of adults, and the extremely limited number of specimens cannot be considered as a representative sample of these ancient populations (Finch 2010b, p. 366). Nor do we know the typical diet and level of physical activity. Further work may yield more data on age and vascular risk factors in these and other ancient populations. However, given the haphazard survival of specimens, it seems unlikely that the few samples available from the tens to hundreds of thousands in these populations of each dynastic period will ever meet current standards for epidemiological studies. The findings of advanced atherosclerosis in ancient mummies must be regarded as case studies, rather than meaningful population samples.

Diet, Infections, and Inflammation in Human Evolution

To consider our evolutionary past in terms of inflammation and diet, I suggest a new framework to explain how humans evolved uniquely long LE among the primates. While hard evidence is currently lacking, I proceed in the spirit of natural philosophy to propose a new set of questions, some of which may lead to testable hypotheses.

While our larger brains and longer postnatal maturation have received most attention in evolutionary studies, the mortality patterns after puberty in humans also differ strikingly from those of the great

apes in the much lower values and in the delayed acceleration during adult aging (Hill et al. 2001; Finch 2010a) (fig. 2B). The lower mortality of human juveniles and young adults under pre-industrial conditions as compared with that of feral chimpanzees suggests our greater resistance to infections. I propose that several environmental and foraging factors were important in the genetic basis for evolving lower basal mortality through their interactions with chronic inflammation: *dietary* fat and caloric content; *infections* from pathogens ingested from carrion, from exposure to excreta, and *non-infectious inflammagens* such as those in aerosols and in cooked foods. I suggest that humans have had far greater exposure to these inflammatory factors than great apes. These pro-inflammatory factors would be expected to increase mortality and shorten life expectancy, yet humans evolved lower mortality and longer lifespans even in highly inflammatory environments.

The great ape LE is about 15 years, and the lifespan rarely exceeds 50 years, whether in natural habitats or in captivity with improved diet, veterinary care, and absence of predators (Goodall 1986; Hill et al. 2001; Finch 2010a; Gurven and Kaplan 2007; Finch and Austad 2011). Under conditions of natural mortality, in which infections are the dominant proximal cause of death, chimpanzees and humans show similar levels of neonatal mortality, 10%-35% (fig. 2B). However, there are two striking differences in mortality patterns. The first emerges at about puberty, when mortality rates tend to be lowest: chimpanzees show about twofold higher baseline mortality as juveniles and young adults than pre-industrial human populations including eighteenth-century Sweden and twentieth-century hunter-foragers (Finch 2010a), based on data in Hill et al. (2001), Gurven and Kaplan (2007), and Hawkes et al. (2009). Subsequently, acceleration of mortality rates occurs 10–20 years earlier in chimpanzees than in human populations. Under conditions of natural mortality, infections are the main cause of death in chimpanzees and hunter-foragers (reviewed in Finch 2010a, p. 1720). Curiously, chimpanzees under modern husbandry have low incidence of major modern human diseases of aging such as cancer and ischemic vascular disease, and lack altogether Alzheimer-like neurodegeneration (Austad and Finch 2011; Finch 2010a; Varki et al. 2011).

Human diets have undergone huge changes. Our preferred diets with 20%–40% fat by dry weight far exceed the natural fat intake of great apes, by an estimated tenfold (Finch and Stanford 2004; Stanford and Bunn 2001). High fat intake is proinflammatory in many settings. While most of the fruits and leaves eaten have negligible cholesterol and are low in unsaturated fatty acids, some oily nuts are consumed, e.g., Panda nut. Additionally, chimps and other great apes, particularly female chimpanzees, avidly forage insect larvae. Hunting of

small mammals and considerable meat consumption are observed in some chimpanzee communities, but are rare in neighboring communities, as well as in other great apes. Thus, it is a working hypothesis that the last shared ancestor had a low-fat diet like that of the present great apes. Dentition would be informative about the diet, but the earliest chimpanzee fossil teeth in the Rift Valley date from only 500,000 YBP (McBrearty and Jablonski 2005).

Besides fat and cholesterol, mammalian prey tissues contain many infectious pathogens. For example, red colobus monkeys, a favorite prey-food of some chimpanzee communities, carry the Ebola virus, which has infected chimpanzee populations in proportion to their consumption (Formenty et al. 1999). Carrion scavenging would have exposed ancestral humans to numerous other infectious pathogens (Finch and Stanford 2004). The tapeworm *Taenia* evolved infectious cycles with human-specific hosts during the past 1.7 million years (Hoberg 2006). This date is consistent with evidence for scavenging by early humans from bone cuts about 2 MYA (Plummer 2004). Chimpanzees also occasionally scavenge carcasses (Muller et al. 1995; Watts 2008). Organized hunting of large animals is not documented until much later, ca. 400,000 YBP, with handax flaking at Boxgrove (Iovita and McPherron 2011; Roberts and Parfitt 1999) and shafted wooden spears and butchered remains of large mammals at Schoeningen (Thieme 1997).

Dust and pollen inhalation is another possible source of chronic inflammation, which has been neglected in discussions of paleopathology. The hazards of dust inhalation are shown in twenty-first-century Spain, where seasonal intrusions of 2.5 micron Sahara dust particles are associated with surges of mortality among the elderly (Jiménez et al. 2010; Maté et al. 2010). Dust particles rapidly penetrate lung alveoli, causing local inflammation and adversely impacting lung, heart, and circulation. Moreover, allergenic pollen from grasses and trees can cause respiratory distress during aerobic exercise (Hellenius et al. 2005). Ample geologic evidence shows surges of pollen and aerosols during human evolution through climate-driven shifts in vegetation and through volcanic activity.[2] Within the last 3 MY, East Africa has undergone major aridification, with shifts in vegetation from closed canopy forest to open grass- and shrub-land savannahs (Cerling et al. 2011; Feakins et al. 2005; Bonnefille 2010). Unlike tropical trees, grasses are major sources of pollen (Dupont and Wyputta 2003). Thus, increased pollen exposure may have been encountered as grasslands expanded. Arid areas are also major dust sources (Prospero et al. 2002). The aridification of

[2]The geologic basis for this section was developed in discussion with Sarah Feakins (USC).

the East African hominin sites is amply documented by an increase in wind-blown dust reaching marine sediments (deMenocal 1995) and by the carbon isotope ratios in paleosols that distinguish woodland and grassland (Cerling et al. 2011). These changes in foliage varied in complex and regionally diverse ways during early human evolution, which is increasingly recognized to have involved southern Africa as well as the upper Rift Valley (Levin et al. 2011). After 3 MYA in the Rift Valley and elsewhere in Africa (Wood and Lonergan 2008; White et al. 2009), hominins would have been exposed to seasonal surges in airborne dust and pollen. Fossil bovids and rodents show shifts to arid-adapted species after 2.7 MYA (Vrba 1995; Bobe and Behrensmeyer 2004). The increase of bovids ca. 1.7 MYA precedes the bifacial hand axes (Acheulian tools, ca 1.4 MYA).

Volcanic aerosols also merit consideration. Major surges of explosive volcanic activity at 4, 2.5, and 1.5 MYA in the Rift Valley are well documented from marine sediments (Feakins et al. 2007) in amounts that imply high density aerosols (S. Feakins, pers. comm.) in regions inhabited by early hominins (Feibel and Brown 1989; Feibel 1999). Volcanic aerosols can cause extensive mortality from inhalation of particulate matter and sulfur dioxide, as in the Laki eruption of 1783–84, which caused 10%–20% excess mortality in Iceland and England (Schmidt et al. 2011).

The clinical observations on pollen and dust inhalation discussed above are relevant to the evolution of human running and fast-walking as part of our bipedalism: ergonomic analysis of fossils suggests that the skeletal capacity for long-stride endurance running may be unique to the genus *Homo*: no great ape or other primate has the capacity for endurance running or walking (Bramble and Lieberman 2004; Carrier 1984; Pontzer et al. 2010; Ruxton and Wilkinson 2011). As discussed in these references, the evolution of long-distance running has been considered as adaptive for scavenging and hunting. Besides numerous anatomical changes to support long-stride walking and running (musculo-skeletal, sweat glands, hair), I suggest that the immune system evolved to cope with the increased inhalation of dust, pollen, and volcanic ash. These concepts could be developed further with estimations of the aerosol load from geologic data. This discussion may also be considered in relation to Raymond Dart's (1925) proposal that human evolution of bipedalism and hunting was shaped by the savannah. Although the "savannah hypothesis" is being challenged (White et al. 2009), evidence is consistent for the progressive expansion of open environments with arid grasslands during the last 3 million years (Cerling et al. 2011).

Smoke from domestic fire contributed additional inflammagens.

Controlled use of fire is documented by about 0.5 MYA in *H. erectus*, a predecessor of *H. sapiens* and *H. Neanderthalensis* (Roebroeks and Villa 2011). The regular use of fire continued in both lineages. Wrangham and Conklin-Brittain (2003) proposed that cooking increased the nutritional yield of meat as well as tubers. Moreover, cooking would also benefit energy and immune resources by killing off parasites such as worms that consume host nutrients and impair childhood growth (Finch 2007). However, there is no evidence for cooking until much later, about 20,000 YBP, at the Ohalo II site near the Sea of Galilee, where wild grains were stone-ground and charred grains were associated with hearths (Piperno et al. 2004). Even earlier, 30,000 YBP, starch grains have been found on human-made grinding platforms in Europe, but were not associated with fire (Revedin et al. 2010).

Domestic fire has many advantages for cooking, heating, and tool making. Moreover, domestic smoke from smoldering twigs, grass, or dung is traditionally used to suppress insects in dwellings throughout the world (Ziba et al. 1994; Biran et al. 2007). However, chronic smoke inhalation from biomass fuel smoke (indoor air pollution) causes pulmonary and vascular damage (hut lung syndrome) (Fullerton et al. 2008; Bruce et al. 2000). I suggest indoor smoke inhalation is an ancient human environmental exposure. In the large Neolithic town of Çatalhöyük on the southern Anatolian plateau (9500–8000 YBP), human burials showed sooty particles on the inner surfaces of ribs, evidently particles trapped by lung tissues that had dried against the ribs (Finch 2007, p. 400; Andrews et al. 2005). The expanding use of domestic fire since 400,000 YPB (Roebroeks and Villa 2011) implies increased exposure to indoor smoke, especially in the colder temperate zones where warmth was critical. Besides carbon particles, endotoxins are found in wood smoke, as well as in smoke from dung, which is widely used as a fuel outside of the developed world. Levels of endotoxin during cooking over biomass fires can reach a thousandfold above the typical background in suburban North American households (Semple et al. 2010). Thus, the progressive use of fire after 400,000 YBP introduced a new level of exposure to environmental inflammagens.

Moreover, cooking itself produces inflammagens: browning and charring during cooking cause glyco-oxidation through non-enzymatic chemistry. These complex Amadori-Maillard products are also produced at slow levels throughout life from glucose in our tissue, where they are known as advanced glycation end products (AGEs) of great significance to aging because AGEs cross-link collagen and other long-lived proteins (Monnier et al. 1984). In rodent models and human dietary crossover studies, dietary AGEs are proinflammatory, proatherogenic, and prothrombotic, and stress or damage kidney and pancreatic beta-cells

(Uribarri et al. 2010; Striker et al. 2009). Thus, while cooked foods have fewer living pathogens, the cooking process introduced new inflammagens not experienced by primate ancestors (Finch 2010a). On the other hand, cooking increases the digestibility of plant foods, as well as inactivating heat-sensitive toxins in tubers. De Bry (1994) suggested that early humans used browning (Amadori-Maillard products) to assure sufficient cooking.

Exposure to excreta is another fundamental environmental difference between modern *H. sapiens* and the great apes. In their largely woodland habitats, the great apes have minimal exposure to excreta. Chimpanzees and other great apes make individual night nests, typically left behind each morning after voiding (Goodall 1986, p. 208; Llorente Caño 2004). In Kibale, Uganda, traces of urine and feces were found in $< 20\%$ of the chimpanzees' arboreal night nests (on the periphery of the nest) that were inspected by climbing (Llorente Caño 2004). However, exposure of the apes to these traces may be limited by the irregular reuse of nests (14% consecutive night nest reuse, ca. 1 in 7 nights). The low frequency of nest reuse in chimpanzees is associated with relocation for foraging needs and social behavior (Hernandez-Aguilar et al. 2009), which I suggest would have an incidental, secondary benefit to hygiene. Anecdotal observations suggest that adult chimpanzees fastidiously avoid contact with excreta (Goodall ibid.), as do orangutans (Carel van Schaik, pers. comm.). However, these hygienic behaviors do not prevent infections altogether, and diarrhea is said to be "common" in wild chimpanzees (Goodall 1986, pp. 93–96). The protozoan *Cryptosporidium*, which causes transient diarrhea, is transmitted by a fecal-oral route (González-Moreno et al., in press). Quantitative data are needed to evaluate the relative daily exposure to excreta in the great apes vs. pre-industrial forager-hunters. Anthropologists I've asked agree from their field studies of traditional hunter-gatherer-forager-farmers that daily exposure to feces is extensive and unavoidable in the villages or semi-permanent settlements. All ages frequently incur diarrhea, and water is usually contaminated by bacteria and parasites. Exposure must be even greater in permanent villages and towns, where raw sewage ran through the streets until recently throughout the world. Sadly for science (on many accounts), the dwindling natural habitat of feral apes may preclude meaningful data on fecal contamination of their drinking water sources.

Another factor in the exposure to excreta is that humans have a higher density of young in their groups because of shorter intervals between births. Under natural fertility, humans are typically weaned by 2–3 years vs. the great apes' weaning at 5 years or longer, at ages when the first adult molars are emerging (Finch 2007, p. 382; Bogin 1999;

Hrdy 2010; Robson and Wood 2008). The earlier weaning of humans might also reduce maternal protection from infections. Moreover, transmission of worms also increases in children after weaning (Drake and Bundy 2001). The higher density of young in humans as compared with that in the chimpanzee family groups would further increase the community load of infections. Recognizing gaps in data, we may still reasonably consider that the common great ape had a much lower exposure to excreta than most human populations before the twentieth century.

While prehistoric hygiene is undocumented, there are archeological indications for a progressive separation of garbage from living and cooking space in pre-Neolithic Natufian settlements (Jordan Valley, 13,000 YBP) (Finch 2007, p. 399). In the Neolithic proper, the town of Çatalhöyük (see above) had clean and dirty areas in its hundreds of apartments (Hodder 2005, 2006; Finlayson et al. 2011). Fecal bile acid residues also show separation of human and animal excreta (Bull et al. 2005). This archeological site is not far from sites of cereal domestication ca. 11,000 YBP.

Glutens, an important current intestinal inflammagen, also entered the human scene by the growing consumption of cereals during the Neolithic (and possibly long before domestication). While gluten peptides are valuable for giving dough its elasticity, these peptides resist digestion by gut enzymes because of their high content of proline and hydrophobic amino acids. A substantial fraction of modern adults incur chronic intestinal inflammation from T-cell reactions to gluten, which reaches clinical grade in celiac disease. Gluten and other cereal proteins are thus another dietary source of inflammagens novel to human evolution, and may have been encountered before the Neolithic, from evidence of residues in grinding stones (see above). Countering the dietary inflammagens from cooking (AGEs) and glutens, human diets introduced some anti-inflammatory factors (Accomando et al. 2010; Calder et al. 2009; Finch 2007): the scattered literature includes salicylates (some fruit skins, willow bark), polyphenols (curcumin), and omega-3 polyunsaturated fatty acids.

Human body size changes give further clues about the growing load of infection and inflammation. From skeletal data representing 60,000 to 10,000 YBP, adult size shrank progressively by about 3 kg/10,000 years (fig. 7, based on Ruff et al. 1997). I hypothesize that this reduction indicates growth limitations from an increasing load of infections and nutritional limitations. Among the many caveats are growth impairments from climate and genotype (Auerbach and Ruff 2010). During the past 200 years, the reverse happened in developing nations: as the load of infections diminished, adult height grew (fig. 3A), while transient

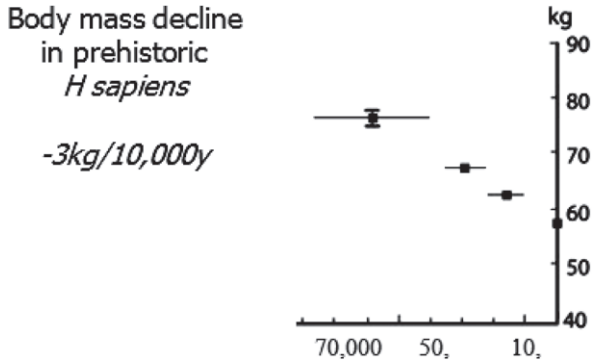

FIGURE 7. Adult body size since 60,000 years. Adult body mass decreased progressively during the past 60,000 years up to the onset of the Neolithic. I hypothesize that this decrease is associated with increased load of infections and inflammation associated with increasing population density. Based on skeletal data (regraphed from Ruff 1997; adapted from Finch 2007 fig. 6.7, p. 399, Elsevier).

infections such as influenza could blunt growth across a birth cohort (fig. 4B).

To stimulate further discussion of these complex changes, I propose seven ecological stages in human evolution, distinguished by inflammatory exposure during human evolution (table 1). This framework extends forward into the twenty-first century to include current trends for obesity, population growth, and global climate deterioration (Stage 7).

Increasing Ozone and Air Pollution; Water Shortages

The human genome was under intense natural selection until mortality from infections became negligible after 1950. The importance of infection-related mortality is shown in the overrepresentation of genes for host defense among those with signals of positive selection; brain and diet are also overrepresented (Wagner 2007). I briefly discuss the *apoE* gene, which illustrates the multiple interactions of diet, inflammation, and infection with many trade-offs and pleiotropies during human evolution.

Apolipoprotein E (apoE) is a major transporter of cholesterol and lipids with multiple roles in systemic lipid metabolism, as well as in brain and immunity. The apoE protein also binds growth factors and other peptides, including the amyloid β-peptide (Aβ) of Alzheimer disease (Mahley and Ralls 2000; Finch 2007; Kuhlmann et al. 2010). Human populations have two major alleles, *ApoE3* and *ApoE4*; *ApoE3* is the most prevalent in all populations; *apoE4* varies widely, over a range of <5% to nearly 50% (Corbo and Scacchi 1999; Singh et al.

TABLE 1. Ecological Stages with Increasing Dietary Fat and Exposure to Infections and Inflammagens

Stage	*Ecology/ Group Size*	*Diet*	*Infection/ Inflammagen Exposure*
1: 4–6 MYA: ancestral ape	Forest-savannah*/ small groups	Low intake of saturated fats	Low exposure to excreta
2: 4–0.5 MYA: hominins/ early *Homo*	Forest–savannah/ small groups		Increasing exposure to infections from excreta & carrion; increased exposure to pollen and dust
3: 500,000–15,000 YBP: *H. ergaster* to *H. Sapiens* pre-Neolithic	Varied-temperate zone/larger groups	Increased meat consumption	Domestic fire & smoke
4: 12,000–150 YBP: *H. sapiens*, Neolithic	Permanent settlements/ larger groups	Cereal and milk from domestic crops and animals	Intense exposure to human and domestic animal excreta and parasites
5: 1800–1950: Industrial age	90% permanent homes, high density	Improving nutrition year around	Improving sanitation and hygiene
6: 1950–2010	Increasing urbanization	Increasing fat and sugar consumption; decreasing physical activity; increasing obesity	Public health-hygiene; reduced infections and parasites; vaccination/ antibiotics, statins
7: 21st century	90% urban; very high density		Increasing ozone and air pollution; water shortages

* As discussed above, open environments increased throughout hominin sites with regional variations in eastern and southern Africa. The habitat of the shared ancestor could have resembled any of the present habitats of chimpanzees and other great apes, from rainforest to dry forest and savannah. Because early *Homo* fossils are found in the same region and strata of the Rift Valley of 0.5 MYA, McBrearty and Jablonski (2005) suggest that ancestral chimpanzees and humans could have had a prolonged coexistence.

2006). *ApoE4* carriers have slightly higher blood total cholesterol and slightly enhanced inflammatory responses (Mahley and Rall 2006; Finch 2007). *ApoE* allele effects are being studied in transgenic mice with targeted replacement of the human alleles. When fed high-fat "Western" diets, *ApoE4* mice develop glucose intolerance with marked adiposity (Arbones-Mainar et al. 2008). This finding supports Corbo and Scacchi's

(1999) hypothesis that *apoE4* is a "thrifty gene" favoring advantageous fat accumulation during times of uncertain nutrition. However, human obesity has not shown consistent apoE allele association.

ApoE4 is also associated with enhanced inflammatory responses (Lynch et al. 2003; Vitek et al. 2009; Zhu et al. 2012), which might be advantageous in the highly infectious environments that prevailed until very recently. Pilot studies of children in Brazilian slums where intestinal disorders are common show protective effects of *ApoE4* on cognitive development (Mitter et al. 2012). In hepatitis virus C (HCV) infections several small clinical samples of *E4* carriers have shown less fibrotic liver damage (Kuhlmann et al. 2010; Wozniak et al. 2002). Thus far, the risk of HCV infection has not been consistently associated with any allele (Kuhlmann et al. 2010).

ApoE alleles also influence diverse chronic non-infectious degenerative diseases and lifespan. In many populations, *ApoE4* carriers have modestly increased risk of coronary disease (Bennet et al. 2007; Stengård et al. 1998). Risks of Alzheimer disease are even higher, up to tenfold for *E4/E4* homozygotes in some populations (Bonomini et al. 2010). *ApoE4* carriers have earlier onset and faster progression during clinical phases, as well as poorer recovery from traumatic brain injury and brain hemorrhage (Verghese et al. 2011; Zhou et al. 2008). Brain development is also influenced by ApoE alleles. By MRI imaging, the entorhinal cortex was thinner in *apoE4* than *-E3* adolescents (Shaw et al. 2007), while transgenic apoE3 mice had greater dendritic complexity and spatial memory, and slower losses during aging than apoE4 mice (Klein et al. 2010; Wang et al. 2005). These regional brain volume differences persist in healthy individuals into the fifties and sixties, when they may be important as neuronal reserves protective against Alzheimer disease and other neurodegenerative changes (Burggrenn et al. 2008; Donix et al. 2010). Not surprisingly, life expectancy is shorter in *E4* carriers. In the Framingham Heart Study, *E4/E4* carriers' life expectancy was 6.4 years shorter than that of non-*E4* carriers (Kulminski et al. 2011). Risks of aging without heart disease varied correspondingly. However, a trade-off was found: while *E3/E4* carriers have earlier onset cardiovascular disease, those surviving to 65 have a lower risk of cancer. This tradeoff joins other pleiotropies of apoE alleles.

Robert Sapolsky, Craig Stanford, and I have argued that *apoE* alleles were mediators of longer lifespans, which evolved despite the increase of fat and exposure to inflammation, which would tend to increase mortality (Finch and Sapolsky 1999; Finch and Stanford 2004). *ApoE4*, the minor allele in all human populations, is considered ancestral in the genus *Homo* (Fullerton et al. 2000). The uniquely human *apoE3* spread about 0.226 MYA (range 0.18–0.58 MYA). The upper

TABLE 2. Species Comparisons of Apolipoprotein E Protein Polymorphisms

Residue number in the mature apoE peptide	61	112	158
Chimpanzee	Threonine	Arginine	Arginine
Human apoE4	Arginine	Arginine	Arginine
Human apoE3	Arginine	Cysteine	Arginine

The chimpanzee apoE protein may function more like human apoE3 in its lipid binding and receptor interactions than apoE4 due to a key amino acid difference at residue 61, a hydrophilic threonine, which is predicted to alter folding of the peptide chains (Finch and Stanford 2004; Finch 2010a). The mouse also has this threonine, whose functional importance to lipid binding was proven by site-directed mutagenesis (Raffaï et al. 2001). Other differences between human and chimp apoE could alter the many functions of apoE, e.g., of the 8 residues that show evidence of positive selection, 4 are in the lipid binding region of the C-terminus (Vamathevan et al. 2008).

limit of this date range precedes the emigration of *H. sapiens* from Africa, while the lower limit overlaps with increased organized hunting of large animals and use of fire during Ecological Stage 3.

The chimpanzee apoE differs from the human in two critical amino acids that are predicted to render its function more apoE3-like (table 2) (Finch and Stanford 2004; Finch 2010a). Though the chimpanzee apoE resembles human apoE4 at 2 amino acid positions, it is predicted to function like the human apoE3 isoform because a further coding difference at residue 61 alters peptide conformation with effects on lipid binding and receptor affinity that resemble apoE3. Raffaï et al. (2001) engineered a transgenic mouse with site-directed mutagenesis of T61R, which produced the predicted apoE3-like lipid binding and functions. These apoE3-like functions could underlie the low levels of Alzheimer's and ischemic heart disease in captive chimpanzees discussed above. The initial step in the evolution of human apoE is predicted to have been replacement of T61R, which should convert to apoE4-like functions. Again, based on transgenic mouse models carrying human *apoE* alleles described above, the proto-human apoE4 genotype would have had heightened inflammatory responses and more efficient fat storage, which I argue would have been adaptive during Phases 2 and 3. A subcellular activity of apoE4 also merits consideration: within the lysosome, apoE4 causes more membrane disruption and leakage than apoE3, because the low lysosome pH allows more peptide chain unfolding, into "molten globule" conformation. Enhanced lysosomal leakage, demonstrated in cell models, may be relevant to Alzheimer pathogenesis (Morrow et al. 2002; Mahley and Huang 2006). Together, the lipid binding and molten globule conformation of apoE4 may be unique to humans. Thus, the apoE allele system has multiple influences relevant to evolution of brain development, metabolic storage, host defense, and longevity.

The Future of Aging

Last, I consider future challenges to the accomplishments in LE that were enabled by improved nutrition, hygiene, and medicine. Stage 7, the twenty-first century, is emerging with increasing global temperatures, increased ozone and air pollution, and shrinking resources of clean water. Urban growth will continue: >80% of the elderly live in cities with high density (WHO 2009). Obesity continues to grow world-wide (Olshansky et al. 2005). Nonetheless, many expect continuing expansion of the remarkable gains in LE. By extrapolating the trajectories of the past century, several leading demographers predicted that "*most babies born since 2000 in France, Germany, Italy, the UK, the USA, Canada, Japan, and other countries with long life expectancies will celebrate their 100th birthdays* [my italics]" (Christensen et al. 2009). Further analysis of mortality trends by the Gompertz model (eq. 1) challenges this prediction (Beltrán-Sánchez, Crimmins, and Finch, in press). The historical trends up through 1990 show that background adult mortality rates are approaching a lower limit of about 0.02% (2/10,000 deaths/y)(Crimmins et al. 2007) (fig. 8). The onset of mortality acceleration after age 40 has not shown any evidence of delay. On the contrary, the faster acceleration against a lower background mortality defines its onset more clearly by the age of 40. The limits of LE can be modeled by modeling with q(0–10) set to 0, which would give a small further increase in the Gompertz slope, and in the "wrong direction" to increase lifespan. For example, in a population of 10 billion, the modal survival age would be about 80 for men and 85 for women. The increases of LE for women are progressing faster than those for men, because women incur progressively lower baseline mortality and faster mortality accelerations. These two parameters have changed less for men in the twentieth century (Beltrán-Sánchez et al., in press).

While the Gompertz coefficients predict further increases in median LE into the twenty-first century, the maximum lifespan (Lmax) will increase much less. The Gompertz formula for mortality rate (eq. 1) may be integrated to obtain the fraction surviving as a function of age (eq. 2) (Finch et al. 1990).

$$S(x) = \exp\{[A/G][1 - \exp(Gx)]\} \qquad \text{Eq. 2}$$

The Lmax is approximated by the age x when a population of size N has a single survivor ($1/N$). Because solving for N involves ln[ln], population size has a minor effect on Lmax for most countries. Again, for a world population of 10 billion, the oldest survivors (maximum lifespan) would be 113 years for men and 120 years for women (Beltrán-Sánchez, Crimmins, and Finch, in press). These predictions closely match the current record lifespans of Harold Martinsen (115 years) and Jeanne Calment (122 years).

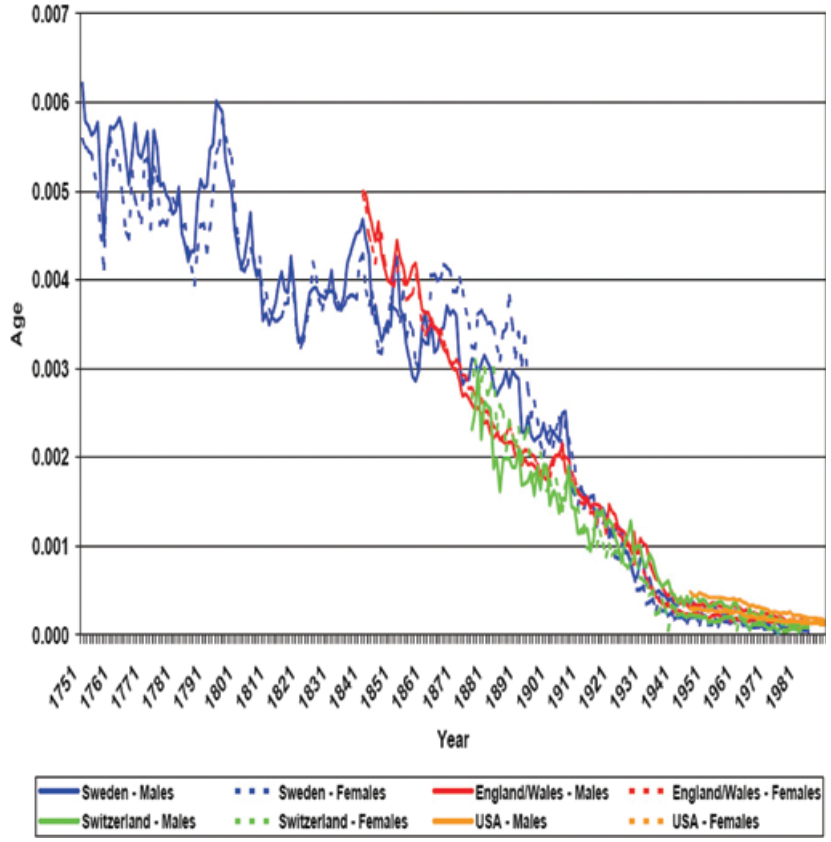

FIGURE 8. Age-specific mortality (Mortality Phase 2). Age-specific mortality declines sharply after birth to a minimum level at about the onset of puberty, which persists up through about age 40 (Mortality Phase 2). After age 40, mortality rates accelerate (Phase 3); see figure 2. Phase 2 may be approaching a pragmatic lower limit of 2 deaths/10,000/year, due to rare accidents (Crimmins et al. 2007 Pop. Assoc. America).

Given the approach to a lower limit to background mortality, the only escape from these limiting values of LE and Lmax would theoretically come from two possibilities: (1) slowing the Gompertz acceleration or (2) delaying the mortality rate acceleration to later ages (or in some combination). Some rodent genotypes do model these possibilities: caloric restriction extends LE and Lmax of some genotypes by slowing the Gompertz acceleration; most of these studies also show higher background mortality (Finch 2007, p. 347; Finch 1990, pp. 507–09), consistent with Strehler-Mildvan relationships. The possibility of delayed mortality acceleration is modeled by two long-lived mouse mutants, the pituitary dwarf mouse (*Pit-1*), which lacks growth hormone

(Flurkey et al. 2001) and the mCAT transgenic (Schriner et al. 2005), which overexpresses mitochondrial catalase. Neither caloric restriction nor deficiencies in growth hormone has been shown to increase human lifespan.

Two global trends also challenge the prediction of continuing increase in human longevity: the global increase of obesity and the global environmental deterioration in association with climate changes. Because obesity is well recognized as a public health liability and risk factor in morbidity, I will focus on climate deterioration. Recent reports on climate change from the U.S. National Academy of Sciences (Anonymous 2010a,b) noted briefly that the elderly are among disadvantaged populations with particular vulnerability. An obvious consequence of global warming trends is that regional heat waves are predicted to become more frequent and intense. The killer summers of 1995 (U.S.) and 2002 (Europe) document the acute vulnerability of the elderly to heat waves. Continuing urbanization will bring even more elderly to cities, which are warmer by several °C than the countryside ("urban heat islands"). Moreover, many elderly cannot afford housing with air-conditioning.

Climate warming alone increases ground-level ozone (Anonymous 2010a,b), which has direct adverse effects on cardio-pulmonary functions (Alexeeff et al. 2008). Western Europe and Southern California are predicted to incur up to 30 more days/year of hazardous ozone by 2050 (www.arb.ca.gov/research/apr/past/04-349.pdf; Varotsos et al. 2011). Ozone notably exacerbates cardiac arrhythmias and other cardiopulmonary dysfunctions prevalent among the elderly. Moreover, 10 ppb elevations of ozone were associated with cognitive deficits during middle age across the U.S., equivalent to accelerating "normative aging" by 4 years (Chen 2009). Ozone also increases during episodes of air stagnation (Valente et al. 1998), which are predicted to become more frequent (Anonymous 2010a,b). The total impact of ozone goes beyond direct effects because of its chemical role in smog. There are also potential feedback loops because trophosphere ozone acts as a greenhouse gas.

Although the most developed countries have lowered their emissions from fossil fuels, the situation is darker in the developing world, where there is an increase in coal use for power, particularly in the Asia-Pacific region, and for vehicular transport. Gains in life expectancy from lower infections and improved diet in many developing countries will be challenged by local levels of air pollution. For example, traffic-related air pollution is the leading cause ("population attributable fraction") of heart attacks in a meta-analysis of 36 epidemiological studies (Nawrot et al. 2011). Associations of vascular disease with vehicular emissions are also well documented. In longitudinal studies

of Los Angeles Basin residents, the rate of carotid thickening maps with local air pollution gradients (Kunzli et al. 2010). In Los Angeles (Linn et al. 2000) and Hong Kong (Ko et al. 2007), smog derived from vehicular emissions is associated with transient cardio-pulmonary conditions and increased hospital admission. The particular impact of vehicular emissions on the health of the elderly is documented in Southern California nursing homes, where cardiovascular risk factors scale with the levels of indoor air pollutants derived from vehicular emissions (Arhami et al. 2010; Delfino et al. 2010). Recent studies from my lab show inflammatory markers of accelerated brain aging in rodents exposed to urban air nanoparticles (Morgan et al. 2011; Zhang et al., in press).

Infections are another danger of global warming (Patz et al. 1996; Anonymous 2010a,b). Emerging shortages of water in many regions threaten hygiene and public health, while the range of insect vectors is expanding with warming trends in temperate zones. Rising sea levels expand the range of brackish waters and marshlands, which support insect populations (Ramasamy and Surendran 2011). These changes have major implications for malaria, dengue, plague, and viral encephalitis (Khasnis and Nettleman 2005). Cholera is also facilitated because *Vibrio cholera* is associated with plankton in brackish waters (Lobitz et al. 2000; Constanti de Magney et al. 2008). The vulnerability of the elderly has been neglected in these discussions. A greater exposure to pathogens, coupled with the well-documented immunosenescence with diminished T-cell responses (Akbar and Henson 2011; Arnold et al. 2011) could increase the burden of infections among seniors. I suggest that the growing density of urban elderly populations could create a reservoir of latent infections from pathogens that are rare in younger groups. These and many other aspects of climate change warrant detailed study for their impact on the expanding elderly populations.

Given the slowness of the development of less-polluting transportation and electricity, we need to examine potential dietary and pharmacological protections. Two studies indicate Vitamin E as a prophylactic for airborne pollutants: Mexico City men who showed nasal mucosal cell dysplasia in association with high levels of urban air pollution improved after 4 months of vitamins A and E (Calderon-Garcidueñas and Roy-Ocotla 1993), whereas vitamin E increased the survival of elderly male Finnish smokers (Hemilä and Kaprio 2009). While tobacco smoke differs from urban air pollution, e.g., in volatile organic compounds, there are shared vascular and cardio-pulmonary effects. A major program of intervention research for air pollution is warranted in view of the slow progress in further improvements of urban air and the high health-care costs of heart and lung dysfunctions in the elderly. Even small benefits would also translate into improved performance in the

workforce of developing nations that lack resources to prioritize these aspects of public health.

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References

Abdelfattah, A., A. H. Allam, S. Wann, R. C. Thompson, G. Abdel-Maksoud, I. Badr, H. A. Amer, A. E. El-Din, C. E. Finch, M. I. Miyamoto, L. Sutherland, J. D. Sutherland, and G. S. Thomas. 2012. Atherosclerotic cardiovascular disease in Egyptian women: 1570 BCE–2011 CE. *International Journal of Cardiology*: in press.

Accomando, S., V. Pellitteri, and G. Corsello. 2010. Natural polyphenols as anti-inflammatory agents. *Frontiers in Bioscience* 2:318–31.

Akbar, A. N., and S. M. Henson. 2011. Are senescence and exhaustion intertwined or unrelated processes that compromise immunity? *Natural Reviews Immunology* 1:289-95.

Alexeeff, S. E., A. A. Litonjua, R. O. Wright, A. Baccarelli, H. Suh, D. Sparrow, P. S. Vokonas, and J. Schwartz. 2008. Ozone exposure, antioxidant genes, and lung function in an elderly cohort: VA normative aging study. *Occupational and Environment Medicine* 65:736–42.

Allam, A. H., R. C. Thompson, L. S. Wann, M. I. Miyamoto, A. H. Nur El-Din, G. A. El-Maksoud, Al-Tohamy, M. Soliman, I. Badr, H. A. El-Rahman Amer, M. L. Sutherland, J. D. Sutherland, and G. S. Thomas. 2011. Atherosclerosis in ancient Egyptian mummies: The Horus study. *Journal of the American College of Cardiology Cardiovascular Imaging* 4:315–27.

Almond, D. 2006. Is the 1918 influenza pandemic over? Long-term effects of in utero influenza exposure in the post-1940 US population. *Journal of Political Economics* 114:672–712.

Almond, D., and B. Mazumder. 2005. The 1918 influenza pandemic and subsequent health outcomes: An analysis of SIPP data. *American Economic Review* 95:258–82.

Anonymous. 2010a. *Adapting to the Impacts of Climate Change*. Washington, D.C.: National Academies Press.

Anonymous. 2010b. *Advancing the Science of Climate Change*. Washington, D.C.: National Academies Press.

Arhami, M., M. C. Minguillón, A. Polidori, J. J. Schauer, R. J. Delfino, and C. Sioutas. 2010. Organic compound characterization and source apportionment of indoor and outdoor quasi-ultrafine particulate matter in retirement homes of the Los Angeles Basin. *Indoor Air* 20:17–30.

Armour-Chelu, M., P. Andrews, and R. L. Bernor. 2005. Further observations on the primate community at Rudabánya II (late Miocene, early Vallesian age), Hungary. *Journal of Human Evolution* 49:88–98.

Arnold, C. R., J. Wolf, S. Brunner, D. Herndler-Brandstetter, and B. Grubeck-Loebenstein. 2011. Gain and loss of T cell subsets in old age—age-related reshaping of the T cell repertoire. *Journal of Clinical Immunology* 31:137–46.

Auerbach, B. M., and C. B. Ruff. 2010. Stature estimation formulae for indigenous North American populations. *American Journal of Physical Anthropology* 141:190–207.

Barker, D. J. 2007. The origins of the developmental origins theory. *Journal of Internal Medicine* 261:412–17.

Barker, D. J., P. D. Gluckman, K. M. Godfrey, J. E. Harding, J. A. Owens, and J. S. Robinson. 1993. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 341: 938–41.

Barker, D. J., and C. Osmond. 1986. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1:1077–81.

Barker, D. J., P. D. Winter, C. Osmond, B. Margetts, and S. J. Simmonds. 1989. Weight in infancy and death from ischaemic heart disease. *Lancet* 2:577–80.

Beltrán-Sánchez, H., E. M. Crimmins, and C. E. Finch. 2012. Early cohort mortality predicts the cohort rate of aging; An historical analysis. *Journal of Developmental Origins of Adult Health and Disease*: in press.

Bennet, A. M., E. Di Angelantonio, Z. Ye, F. Wensley, A. Dahlin, A. Ahlbom, B. Keavney, R. Collins, B. Wiman, U. de Faire, and J. Danesh. 2007. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *Journal of the American Medical Association* 298:1300–11.

Biran, A., L. Smith, J. Lines, J. Ensink, and M. Cameron. 2007. Smoke and malaria: Are interventions to reduce exposure to indoor air pollution likely to increase exposure to mosquitoes? *Transactions of the Royal Society of Tropical Medicine and Hygiene* 101:1065–71.

Block, M. L., and L. Calderón-Garcidueñas. 2009. Air pollution: Mechanisms of neuroinflammation & CNS disease. *Trends in Neuroscience* 32:506–16.

Bobe, R., and K. Behrensmeyer. 2004. The expansion of grassland ecosystems in Africa in relation to mammalian evolution and the origin of the genus Homo. *Palaeogeography, Palaeoclimatology, Palaeoecology* 207:399–420.

Bogin, B. 1999. Evolutionary perspective on human growth. *Annual Reviews of Anthropology* 28:109–56.

Bonnefille, R. 2010. Cenozoic vegetation, climate changes and hominid evolution in tropical Africa. *Global and Planetary Change* 72:390–411.

Bonomini, F., F. Filippini, T. Hayek, M. Aviram, S. Keidar, L. F. Rodella, R. Coleman, and R. Rezzani. 2010. Apolipoprotein E and its role in aging and survival. *Experimental Gerontology* 45:149–57.

Bramble, D. M., and D. E. Lieberman. 2004. Endurance running and the evolution of Homo. *Nature* 432:345–52.

Bruce, N., R. Perez-Padilla, and R. Albalak. 2000. Indoor air pollution in developing countries: A major environmental and public health challenge. *Bulletin of the World Health Organization* 78:1078–92.

Brundage, J. F., and G. D. Shanks. 2008. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. *Emerging Infectious Disease* 4:1193–99.

Bruschi, F., M. Masetti, M. T. Locci, R. Ciranni, and G. Fornaciari. 2006. Short report: Cysticercosis in an Egyptian mummy of the late Ptolemaic period. *American Journal of Tropical Medicine and Hygiene* 74:598–99.

Bull, I. D., M. M. Elhmmali, P. Perret, W. Matthew, D. J. Roberts, and R. P. Evershed. 2005. Biomarker evidence of fecal deposition in archeological sediments at Çatalhöyük. In *Inhabiting Çatalhöyük: Reports from the 1995–1999 seasons. McDonald Institute for Archeological Research/British Institute for Archeology at Ankara Monograph* 415–20.

Canudas-Romero, V. 2008. The modal age at death and the shifting mortality hypothesis. *Demographic Research* 19:1179–1204.

Carrier, D. R. 1984. The energetic paradox of human running and hominid evolution. *Current Anthropology* 25:483–95.

Case, A., and C. Paxson. 2010. Causes and consequences of early-life health. *Demography* 47 Suppl.:S65–85.

Caspari, R., and S. H. Lee. 2004. Older age becomes common late in human evolution. *Proceedings of the National Academy of Sciences* 101:10895–900.

Cerling, T. E., J. G. Wynn, S. A. Andanje, M. I. Bird, D. K. Korir, N. E. Levin, W. Mace, A. N. Macharia, J. Quade, and C. H. Remien. 2011. Woody cover and hominin environments in the past 6 million years. *Nature* 476:51–56.

Chen, J. C., and J. Schwartz. 2009. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. *Neurotoxicology* 30:231–39.
Christensen, K., G. Doblhammer, R. Rau, and J. W. Vaupel. 2009. Ageing populations: The challenges ahead. *Lancet* 374:1196–208.
Constantin de Magny, G., R. Murtugudde, M. R. Sapiano, A. Nizam, C. W. Brown, A. J. Busalacchi, M. Yunus, G. B. Nair, A. I. Gil, C. F. Lanata, J. Calkins, B. Manna, K. Rajendran, M. K. Bhattacharya, A. Huq, R. B. Sack, and R. R. Colwell. 2008. Environmental signatures associated with cholera epidemics. *Proceedings of the National Academy of Sciences* 105:17676–81.
Corbo, R. M., and R. Scacchi. 1999. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a "thrifty" allele? *Annals of Human Genetics* 63:301–10.
Crimmins, E. M., and H. Beltrán-Sánchez. 2011. Mortality and morbidity trends: Is there compression of morbidity? *Journals of Gerontology: Series B Psychological Science and Social Sciences* 66:75–86.
Crimmins, E. M., G. Drevenstedt, and C. E. Finch. 2007. Evolution of the human mortality curve: Changes in the age of minimum mortality. *Population Association of America*: http://paa2007.princeton.edu.
Crimmins, E. M., and C. E. Finch. 2006a. Infection, inflammation, height, and longevity. *Proceedings of the National Academy of Sciences* 103:498–503.
Crimmins, E. M., and C. E. Finch. 2006b. Commentary: Do older men and women gain equally from improving childhood conditions? *International Journal of Epidemiology* 35:1270–71.
David, A. R. 1979. *The Manchester Museum Mummy Project*. Leeds, England: W. S. Maney & Son LTD.
David, A. R., A. Kershaw, and A. Heagerty. 2010. Atherosclerosis and diet in ancient Egypt. *Lancet* 375:718–19.
Delfino, R. J., T. Tjoa, D. L. Gillen, N. Staimer, A. Polidori, M. Arhami, L. Jamner, C. Sioutas, and J. Longhurst. 2010. Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. *Epidemiology* 21:396–404.
deMenocal, P. B. 1995. Plio-Pleistocene African climate. *Science* 270:53–59.
Doblhammer, G., and J. W. Vaupel. 2001. Lifespan depends on month of birth. *Proceedings of the National Academy of Sciences* 98:2934–39.
Donix, M., A. C. Burggren, N. A. Suthana, P. Siddarth, A. D. Ekstrom, A. K. Krupa, M. Jones, A. Rao, L. Martin-Harris, L. M. Ercoli, K. J. Miller, G. W. Small, and S. Y. Bookheimer. 2010. Longitudinal changes in medial temporal cortical thickness in normal subjects with the APOE-4 polymorphism. *Neuroimage* 53:37–43.
Donoghue, H. D., O. Y. Lee, D. E. Minnikin, G. S. Besra, J. H. Taylor, and M. Spigelman. 2010. Tuberculosis in Dr Granville's mummy: A molecular re-examination of the earliest known Egyptian mummy to be scientifically examined and given a medical diagnosis. *Proceedings of Royal Society Biological Sciences* 277:51–56.
Drake, L. J., and D. A. Bundy. 2001. Multiple helminth infections in children: Impact and control. *Parasitology* 122:S73–81.
Dupont, L. M., and U. Wyputta. 2003. Reconstructing pathways of aeolian pollen transport to the marine sediments along the coastline of SW Africa. *Quaternary Science Reviews* 22:157–74.
Engelman, M., V. Canudas-Romo, and E. M. Agree. 2010. The implications of increased survivorship for mortality variation in aging populations. *Population and Development Review* 36:511–39.
Feakins, S., F. Brown, and P. deMenocal. 2007. Plio-Pleistocene microtephra in DSDP Site 231, Gulf of Aden. *Journal of African Earth Science* 48:341–52.
Feakins, S., P. deMenocal, and T. I. Eglinton. 2005. Biomarker records of Late Neogene changes in East African vegetation. *Geology* 33:977–80.
Feibel, C., F. Brown, and I. McDougall. 1989. Stratigraphic context of fossil hominids from the Omo Group deposits, northern Turkana Basin, Kenya and Ethiopia. *American Journal of Physical Anthropology* 78:595–622.

Feibel, C. S. 1999. Basin evolution, sedimentary dynamics and hominid habitats in East Africa: An ecosystem approach. In *African Biogeography, Climate Change, and Human Evolution*, ed. T. Bromage and F. Schrenk, 276–81. Oxford: Oxford University Press.

Finch, C. E. 2007. *The Biology of Human Longevity.* San Diego: Academic Press.

———. 2010a. Evolution of the human lifespan and diseases of aging: Roles of infection, inflammation, and nutrition. *Proceedings of the National Academy of Sciences* 107:S1718–24.

———. 2010b. Evolving views of ageing and longevity from Homer to Hippocrates: Emergence of natural factors, persistence of the supernatural. *Greece & Rome* 57:355–77.

———. 2010c. Inflammation in aging processes: An integrative and ecological perspective. In *Handbook of the Biology of Aging*, 7th ed., ed. E. Masoro and S. Austad, 275–96. San Diego: Academic Press.

———. 2011. Atherosclerosis is an old disease: Summary of the Ruffer Centenary Symposium, The paleocardiology of ancient Egypt, a meeting report of the Horus Study Team. *Experimental Gerontology* 46:843–46.

Finch, C. E., and S. A. Austad. 2011. Primate aging in the mammalian scheme: The puzzle of extreme variation in brain aging. *AGE* (Special Issue) Nonhuman Primate Models of Aging. *Journal of the American Aging Association*: in press.

Finch, C. E., and E. M. Crimmins. 2004. Inflammatory exposure and historical changes in human life spans. *Science* 305:1736–39.

———. 2005. Author reply to E. Barbi and J. W. Vaupel, Comment on "Inflammatory exposure and historical changes in human life-spans." *Science* 305:1743b.

Finch, C. E., and T. B. Kirkwood. 2000. *Chance, Development, and Aging.* Oxford: Oxford University Press.

Finch, C. E., M. C. Pike, and M. Witten. 1990. Slow mortality rate accelerations during aging in animals approximate that of humans. *Science* 249:902–05.

Finch, C. E., and R. M. Sapolsky. 1999. The evolution of Alzheimer disease, the reproductive schedule, and apoE isoforms. *Neurobiology of Aging* 20:407–28.

Finch, C. E., and C. B. Stanford. 2004. Meat-adaptive genes and the evolution of slower aging in humans. *Quarterly Review of Biology* 79:3–50.

Finch, C. E., and R. E. Tanzi. 1997. Genetics of aging. *Science* 278:407–11.

Finlayson, B., S. J. Mithen, M. Najjar, S. Smith, D. Maričević, N. Pankhurst, and L. Yeomans. 2011. Architecture, sedentism, and social complexity at Pre-Pottery Neolithic A WF16, Southern Jordan. *Proceedings of the National Academy of Sciences* 108:8183–88.

Flurkey, K., J. Papaconstantinou, R. A. Miller, and D. E. Harrison. 2001. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proceedings of the National Academy of Sciences* 98:6736–41.

Formenty, P., C. Boesch, M. Wyers, C. Steiner, F. Donati, F. Dind, F. Walker, and B. Le Guenno. 1999. Ebola virus outbreak among wild chimpanzees living in a rain forest of Côte d'Ivoire. *Journal of Infectious Diseases* 179:S120–26.

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

Franceschi, C. 2007. Inflammaging as a major characteristic of old people: Can it be prevented or cured? *Nutrition Reviews* 65:S173–76.

Fries, J. F. 1980. Aging, natural death, and the compression of morbidity. *New England Journal of Medicine* 303:130–35.

Fullerton, D. G., N. Bruce, and S. B. Gordon. 2008. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 102:843–51.

Gleason, P. P., C. Williams, S. Hrdy, S. C. Hartwig, and D. Lassen. 2005. Medical and pharmacy expenditures after implementation of a cyclooxygenase-2 inhibitor prior authorization program. *Pharmacotherapy* 25:924–34.

Godfrey K. M., P. D. Gluckman, and M. A. Hanson. 2010. Developmental origins of metabolic disease: Life course and intergenerational perspectives. *Trends in Endocrinology and Metabolism* 21:199–205.

Gonzalez-Moreno, O., R. A. Hernandez-Aguilar, A. K. Piel, F. Stewart, M. Gracenea, and J. J. Moore. [2012]. Forthcoming. Prevalence and associated factors of *Cryptosporidium* infections in savanna chimpanzees in Ugalla, western Tanzania.

Goodall, J. 1986. *The Chimpanzees of Gombe*. Cambridge, Mass.: Harvard University, Belknap Press.

Gurven, M., and H. Kaplan. 2007. Longevity among hunter-gatherers: A cross-cultural examination. *Population and Development Review* 33:321–65.

Gurven, M., H. Kaplan, J. Winking, C. E. Finch, and E. M. Crimmins. 2008. Aging and inflammation in two epidemiological worlds. *Journals of Gerontology: Medical Sciences* 63A:196–99.

Gurven, M., H. Kaplan, J. Winking, D. E. Rodriguez, S. Vasunilashorn, J.-K. Kim, C. E. Finch, and E. M. Crimmins. 2009. Inflammation and infection do not promote arterial aging and cardiovascular disease risk factors among lean horticulturalists. *PLoS* One 4:e6590.

Hawkes, K. 2010. Colloquium paper: How grandmother effects plus individual variation in frailty shape fertility and mortality: Guidance from human-chimpanzee comparisons. *Proceedings of the National Academy of Sciences* 107:8977–84.

Helenius, I., A. Lumme, and T. Haahtela. 2005. Asthma, airway inflammation and treatment in elite athletes. *Sports Medicine* 35:565–74.

Hemilä, H., and J. Kaprio. 2009. Modification of the effect of vitamin E supplementation on the mortality of male smokers by age and dietary vitamin C. *American Journal of Epidemiology* 169:946–53.

Hernandez-Aguilar, A. 2009. Chimpanzee nest distribution and site re-use in a dry habitat: Implications for early hominin ranging. *Journal of Human Evolution* 57:350–64.

Herskind, A. M., M. McGue, N. V. Holm, T. I. Sorensen, B. Harvald, and J. W. Vaupel. 1996. The heritability of human longevity: A population-based study of 2872 Danish twin pairs born 1870–1900. *Journal of Human Genetics* 97:319–23.

Hill, K., C. Boesch, J. Goodall, A. Pusey, J. Williams, and R. Wrangham. 2001. Mortality rates among wild chimpanzees. *Journal of Human Evolution* 40:437–50.

Hoberg, E. P. 2006. Phylogeny of Taenia: Species definitions and origins of human parasites. *Parasitology International* 55:S23–30.

Hodder, I. 2004. Women and men at Çatalhöyük. *Scientific American* 290:76–83.

———. 2005. *Inhabiting Çatalhöyük: Reports from the 1995–1999 Seasons by Members of the Çatalhöyük Teams*. London: McDonald Institute Monographs.

———. 2006. *The Leopard's Tale. Revealing the Mysteries of Çatalhöyük*. London: Thames and Hudson.

Hrdy, S. B. 2010. *Mother and Others: The Evolutionary Origins of Mutual Understanding*. Cambridge, Mass.: Harvard University, Belknap Press.

Iovita, R., and S. P. McPherron. 2011. The handaxe reloaded: A morphometric reassessment of Acheulian and Middle Paleolithic handaxes. *Journal of Human Evolution* 61:61–74.

Jiménez, E., C. Linares, D. Martínez, and J. Díaz. 2010. Role of Saharan dust in the relationship between particulate matter and short-term daily mortality among the elderly in Madrid (Spain). *Science of the Total Environment* 408:5729–36.

Kannisto, V. 2000. Measuring the compression of mortality. *Demographic Research* 3.6.

Kaplan, H. S., K. Hill, J. B. Lancaster, and A. M. Hurtado. 2000. A theory of human life history evolution: Diet, intelligence, and longevity. *Evolutionary Anthropology* 9:156–83.

Khasnis, A. A., and M. D. Nettleman. 2005. Global warming and infectious disease. *Archives of Medical Research* 36:689–96.

Kirkwood, T. B., and C. E. Finch. 2002. Ageing: The old worm turns more slowly. *Nature* 419:794–95.

Klein, R. C., B. E. Mace, S. D. Moore, and P. M. Sullivan. 2010. Progressive loss of synaptic integrity in human apolipoprotein E4 targeted replacement mice and attenuation by apolipoprotein E2. *Neuroscience* 17:1265–72.
Ko, F. W., W. Tam, T. W. Wong, D. P. Chan, A. H. Tung, C. K. Lai, and D. S. Hui. 2007. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax* 62:780–85.
Kuhlmann, I., A. M. Minihane, P. Huebbe, A. Nebel, and G. Rimbach. 2010. Apolipoprotein E genotype and hepatitis C, HIV and herpes simplex disease risk: A literature review. *Lipids in Health and Disease* 9:8.
Kulminski, A. M., I. Culminskaya, S. V. Ukraintseva, K. G. Arbeev, L. Arbeeva, D. Wu, I. Akushevich, K. C. Land, and A. I. Yashin. 2011. Trade-off in the effects of the apolipoprotein E polymorphism on the ages at onset of CVD and cancer influences human lifespan. *Aging Cell* 10:533–41.
Künzli, N., M. Jerrett, R. Garcia-Esteban, X. Basagaña, B. Beckermann, F. Gilliland, M. Medina, J. Peters, H. N. Hodis, and W. J. Mack. 2010. Ambient air pollution and the progression of atherosclerosis in adults. *PLoS One* 5:e9096.
Le Bailly, M., S. Mouze, G. C. da Rocha, J. L. Heim, R. Lichtenberg, F. Dunand, and F. Bouchet. 2010. Identification of Taenia sp. in a mummy from a Christian necropolis in El-Deir, Oasis of Kharga, ancient Egypt. *Journal of Parasitology* 96:213–15.
Levin, N. E., F. H. Brown, A. K. Behrensmeyer, R. Bobe, and T. E. Cerling. 2011. Paleosol carbonates from the Omo Group: Isotopic records of local and regional environmental change in East Africa. *Paleogeography, Paleoclimatology, and Paleoecology* 307:75–89.
Linn, W. S., Y. Szlachcic, H. Gong Jr., P. L. Kinney, and K. T. Berhane. 2000. Air pollution and daily hospital admissions in metropolitan Los Angeles. *Environmental Health Perspectives* 108:427–34.
Llorente Caño, M. 2004. Nesting behaviour of the Kanyawara community of chimpanzees. Kibale National Park, Uganda. Ph.D. diss., University of Barcelona, Spain.
Lobitz, B., L. Beck, A. Huq, B. Wood, G. Fuchs, A. S. Faruque, and R. Colwell. 2000. Climate and infectious disease: Use of remote sensing for detection of Vibrio cholerae by indirect measurement. *Proceedings of the National Academy of Sciences* 97:1438–43.
Lynch, J. R., W. Tang, H. Wang, M. P. Vitek, E. R. Bennett, P. M. Sullivan, D. S. Warner, and D. T. Laskowitz. 2003. APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response. *Journal of Biological Chemistry* 278:48529–33.
Magee, R. 1998. Arterial disease in antiquity. *Medical Journal of Australia* 169:663–66.
Mahley, R. W., and Y. Huang. 2006. Apolipoprotein (apo) E4 and Alzheimer's disease: Unique conformational and biophysical properties of apoE4 can modulate neuropathology. *Acta Neurologica Scandinavica, Supplementum* 185:8–14.
Mahley, R. W., and S. C. Rall Jr. 2000. Apolipoprotein E: Far more than a lipid transport protein. *Annual Review of Genomics and Human Genetics* 1:507–37.
Martin, G. M. 2011. Stochastic modulations of the pace and patterns of ageing: Impacts on quasi-stochastic distributions of multiple geriatric pathologies. *Mechanisms of Ageing and Development*: in press.
Maté, T., R. Guaita, M. Pichiule, C. Linares, and J. Díaz. 2010. Short-term effect of fine particulate matter (PM 2.5) on daily mortality due to diseases of the circulatory system in Madrid (Spain). *Science of the Total Environment* 408:5750–57.
Mazumder, B., D. Almond, K. Park, E. M. Crimmins, and C. E. Finch. 2010. Lingering prenatal effects of the 1918 influenza pandemic on cardiovascular disease. *Journal of Developmental Origins of Health and Disease* 1:26–34.
McBrearty, S., and N. G. Jablonski. 2005. First fossil chimpanzee. *Nature* 437:105–08.
Mitter, S. S., R. B. Oriá, M. P. Kvalsund, P. Pamplona, E. S. Joventino, R.M.S. Mota, D. C. Gonçalves, P. D. Patrick, R. L. Guerrant, and A. A. Lima. 2012. Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from Northeast Brazil. *Clinics* 67.1(12): 11–18.

Monnier, V. M., R. R. Kohn, and A. Cerami. 1984. Accelerated age-related browning of human collagen in diabetes mellitus. *Proceedings of the National Academy of Sciences* 81:583–87.

Morens, D. M., J. K. Taubenberger, and A. S. Fauci. 2008. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: Implications for pandemic influenza preparedness. *Journal of Infectious Diseases* 198:962–70.

Morgan, T. E., D. D. Davis, N. Iwata, J. M. Tanner, D. Snyder, Z. Ning, W. Kam, Y. T. Hsu, J. W. Winkler, J. C. Chen, N. A. Petasis, M. Baudry, C. Sioutas, and C. E. Finch. 2011. Glutamatergic neurons in rodent models respond to nanoscale particulate urban air pollutants *in vivo* and *in vitro*. *Environmental Health Perspectives* 119:1003–09.

Morrow, J. A., D. M. Hatters, B. Lu, P. Hochtl, K. A. Oberg, B. Rupp, and K. H. Weisgraber. 2002. Apolipoprotein E4 forms a molten globule. A potential basis for its association with disease. *Journal of Biological Chemistry* 277:50380–85.

Muller, M. N., E. Mpongo, C. B. Stanford, and C. Boehm. 1995. A note on scavenging by wild chimpanzees. *Folia Primatologica* 65:43–47.

Murphy, W. A., Jr., Dz. D. Nedden, P. Gostner, R. Knapp, W. Recheis, and H. Seidler. 2003. The iceman: Discovery and imaging. *Journal of Radiology* 226:614–29.

Nawrot, T. S., L. Perez, N. Künzli, E. Munters, and B. Nemery. 2011. Public health importance of triggers of myocardial infarction: A comparative risk assessment. *Lancet* 377:732–40.

Oeppen, J., and J. W. Vaupel. 2002. Demography. Broken limits to life expectancy. *Science* 296:1029–31.

Olshansky, S. J., D. J. Passaro, R. C. Hershow, J. Layden, B. A. Carnes, J. Brody, L. Hayflick, R. N. Butler, D. B. Allison, and D. S. Ludwig. 2005. A potential decline in life expectancy in the United States in the 21st century. *New England Journal of Medicine* 352:1138–45.

Ortiz, L. A., A. Quan, F. Zarzar, A. Weinberg, and M. Baum. 2003. Prenatal dexamethasone programs hypertension and renal injury in rat. *American Journal of Hypertension* 41:328–34.

Patz, J. A., P. R. Epstein, T. A. Burke, and J. M. Balbus. 1996. Global climate change and emerging infectious diseases. *Journal of the American Medical Association* 275:217–23.

Perez, L., R. Rapp, and N. Künzli. 2010. The Year of the Lung: Outdoor air pollution and lung health. *Swiss Medical Weekly* doi: 10.4414/smw.2010.13129.

Piperno, D. R., E. Weiss, I. Holst, and D. Nadel. 2004. Processing of wild cereal grains in the Upper Palaeolithic revealed by starch grain analysis. *Nature* 430:670–73.

Plummer, T. 2004. Flaked stones and old bones: Biological and cultural evolution at the dawn of technology. *American Journal of Physical Anthropology* 39:118–64.

Pontzer, H., C. Rolian, G. P. Rightmire, T. Jashashvili, M. S. Ponce de León, D. Lordkipanidze, and C. P. Zollikofer. 2010. Locomotor anatomy and biomechanics of the Dmanisi hominins. *Journal of Human Evolution* 58:492–504.

Preston, S. 1976. *Mortality Patterns in National Populations*. New York: Academic Press.

Preston, S., N. Keyfitz, and R. Schoen. 1972. *Causes of Death: Life Tables for National Populations*. New York: Seminar Press.

Prospero, J. M., P. Ginoux, O. Torres, S. E. Nicholson, and T. E. Gill. 2002. Environmental characterization of global sources of atmospheric soil dust identified with the Nimbus 7 Total Ozone Mapping Spectrometer (TOMS) absorbing aerosol product. *Reviews of Geophysics* 40:1–31.

Raffaï, R. L., L. M. Dong, R. V. Farese Jr., and K. H. Weisgraber. 2001. Introduction of human apolipoprotein E4 "domain interaction" into mouse apolipoprotein E. *Proceedings of the National Academy of Sciences* 98:11587–91.

Ramasamy, R., and S. N. Surendran. 2011. Possible impact of rising sea levels on vector-borne infectious diseases. *BioMedCentral Infectious Diseases* 11:18.

Regnström, J., S. Jovinge, P. Båvenholm, C. G. Ericsson, U. De Faire, A. Hamsten, M. L. Hellenius, J. Nilsson, and P. Tornvall. 1998. Helicobacter pylori seropositivity is not associated with inflammatory parameters, lipid concentrations and degree of coronary artery disease. *Journal of Internal Medicine* 243:109–13.

Revedin, A., B. Aranguren, R. Becattini, L. Longo, E. Marconi, M. M. Lippi, N. Skakun, A. Sinitsyn, E. Spiridonova, and J. Svoboda. 2010. Thirty-thousand-year-old evidence of plant food processing. *Proceedings of the National Academy of Sciences* 107:18815–19.

Reyes, S., B. Montull, R. Martínez, J. Córdoba, J. M. Molina, V. Martí, A. Martínez, P. Ramírez, and R. Menéndez. 2011. Risk factors of A/H1N1 etiology in pneumonia and its impact on mortality. *Respiratory Medicine* 105:1404–11.

Reyes-García, V., T. W. McDade, V. Vadez, T. Huanca, W. Leonard, S. Tanner, and R. Godoy. 2008. Non-market returns to traditional human capital: Nutritional status and traditional knowledge in a native Amazonian society. *Journal of Development Studies* 42:217–32.

Roberts, M. B., and S. A. Parfitt. 1999. *Boxgrove: A Middle Pleistocene Hominid Site at Earthen Quarry, Boxgrove, West Sussex*. London: English Heritage.

Robson, S. L., and B. Wood. 2008. Hominin life history: Reconstruction and evolution. *Journal of Anatomy* 212:394–425.

Rockstroh, J., G. Guaraldi, and G. Deray. 2010. HIV and the body: A review of multidisciplinary management. *HIV Medicine* doi:10.1111/j.1468–1293.2010.00859.x.

Roebroeks, W., and P. Villa. 2011. On the earliest evidence for habitual use of fire in Europe. *Proceedings of the National Academy of Sciences* 108:5209–14.

Roemer- und Pelizaeus-Museum, Hildesheim, Germany.

Ruffer, M. A. 1911. On arterial lesions found in Egyptian mummies (1580 BC–535 AD). *Journal of Pathology and Bacteriology* 15:453–62.

Ruxton, G. D., and D. M. Wilkinson. 2011. Thermoregulation and endurance running in extinct hominins: Wheeler's models revisited. *Journal of Human Evolution* 61: 169–75.

Samuelsson, A. M., I. Ohrn, J. Dahlgren, E. Eriksson, B. Angelin, B. Folkow, and A. Holmang. 2004. Prenatal exposure to interleukin-6 results in hypertension and increased hypothalmic-pituitary-adrenal axis activity in adult rats. *Endocrinology* 145:4897–911.

Schmidt, A., B. Ostro, K. S. Carslaw, M. Wilson, T. Thordarson, G. W. Mann, and A. J. Simmons. 2011. Excess mortality in Europe following a future Laki-style Icelandic eruption. *Proceedings of the National Academy of Sciences* 108:15710–15.

Schriner, S. E., N. J. Linford, G. M. Martin, P. Treuting, C. E. Ogburn, M. Emond, P. E. Coskun, W. Ladiges, N. Wolf, H. Van Remmen, D. C. Wallace, and P. S. Rabinovitch. 2005. Extension of murine life span by overexpression of catalase targeted to mitochondria. *Science* 308:1909–11.

Semple, S., D. Devakumar, D. G. Fullerton, P. S. Thorne, N. Metwali, A. Costello, S. B. Gordon, D. S. Manandhar, and J. G. Ayres. 2010. Airborne endotoxin concentrations in homes burning biomass fuel. *Environmental Health Perspectives* 118:988–91.

Shaw, P., J. P. Lerch, J. C. Pruessner, K. N. Taylor, A. B. Rose, D. Greenstein, L. Clasen, A. Evans, J. L. Rapoport, and J. N. Giedd. 2007. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: An observational study. *Lancet Neurology* 6:494–500.

Shi, L., S. E. Smith, N. Malkova, D. Tse, Y. Su, and P. H. Patterson. 2009. Activation of the maternal immune system alters cerebellar development in the offspring. *Brain Behavior and Immunity* 23:116–23.

Shi, L., N. Tu, and P. H. Patterson. 2005. Maternal influenza infection is likely to alter fetal brain development indirectly: The virus is not detected in the fetus. *International Journal of Developmental Neuroscience* 23:299–305.

Shiels, M. S., R. M. Pfeiffer, M. H. Gail, H. I. Hall, J. Li, A. K. Chaturvedi, K. Bhatia, T. S. Uldrick, R. Yarchoan, J. J. Goedert, and E. A. Engels. 2011. Cancer burden in

the HIV-infected population in the United States. *Journal of the National Cancer Institute* 103:753–62.
Stanford, C. B., and H. T. Bunn. 2001. *Meat-Eating and Human Evolution.* Oxford: Oxford University Press.
Stengård, J. H., K. M. Weiss, and C. F. Sing. 1998. An ecological study of association between coronary heart disease mortality rates in men and the relative frequencies of common allelic variations in the gene coding for apolipoprotein. *European Journal of Human Genetics* 103:234–41.
Strehler, B. L., D. D. Mark, A. S. Mildvan, and M. V. Gee. 1959. Rate and magnitude of age pigment accumulation in the human myocardium. *Journals of Gerontology* 14:430–39.
Strehler, B. L., and A. S. Mildvan. 1960. General theory of mortality and aging. *Science* 132:14–21.
Striker, G. E., H. Vlassara, and L. Ferrucci. 2009. Aging and the kidney: Introduction. *Seminars in Nephrology* 29:549–50.
Symonds, C. E., U. Galderisi, and A. Giordano. 2009. Aging of the inceptive cellular population: The relationship between stem cells and aging. *Aging* (Albany, N.Y.) 1:372–81.
Thieme, H. 1997. Lower Palaeolithic hunting spears from Germany. *Nature* 385:807–10.
Trinkaus, E. 2011. Late Pleistocene adult mortality patterns and modern human establishment. *Proceedings of the National Academy of Sciences* 108:1267–71.
Uribarri, J., S. Woodruff, S. Goodman, W. Cai, X. Chen, R. Pyzik, A. Yong, G. E. Striker, and H. Vlassara. 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *Journal of the American Dietetic Association* 110:911–16.
Valente, R. J., R. E. Imhoff, R. L. Tanner, J. F. Meagher, P. H. Daum, R. M. Hardesty, R. M. Banta, R. J. Alvarez, R. T. McNider, and N. V. Gillani. 1998. Ozone production during an urban air stagnation episode over Nashville, Tennessee. *Journal of Geophysical Research* 103:555–68.
Vamathevan, J. V., S. Hasan, R. D. Emes, H. Amrine-Madsen, D. Rajagopalan, S. D. Topp, V. Kumar, M. Word, M. D. Simmons, S. M. Foord, P. Sanseau, Z. Yang, and J. D. Holbrook. 2008. The role of positive selection in determining the molecular cause of species differences in disease. *BiomedCentral Evolutionary Biology* 8:273. doi:10.1186/1471-2148-8-273.
Van Den Biggelaar, A. H., A. J. De Craen, J. Gussekloo, T. W. Huizinga, B. T. Heijmans, M. Frölich, T. B. Kirkwood, and R. G. Westendorp. 2004. Inflammation underlying cardiovascular mortality is a late consequence of evolutionary programming. *FASEB Journal* 18:1022–24.
Varki, A. 2010. Fate of "retired" research chimps. *Nature* 467:1047.
Varki, N. M., E. Strobert, E. J. Dick Jr., K. Benirschke, and A. Varki. 2011. Biomedical differences between human and nonhuman hominids: Potential roles for uniquely human aspects of sialic acid biology. *Annual Reviews of Pathology* 6:365–93.
Varotsos, V., C. Giannakopoulos, and M. Tombrou. 2011. Climate change impact on future air quality in Europe: A two-way approach. *Geophysical Research Abstracts* 13:EGU2011–12062.
Vasunilashorn, S., E. M. Crimmins, J.-K. Kim, J. Winking, M. Gurven, H. Kaplan, and C. E. Finch. 2010. Blood lipids, infection and inflammatory markers in the Tsimane of Bolivia, a highly infected population. *American Journal of Human Biology* 22:731–40.
Vasunilashorn, S., C. E. Finch, E. M. Crimmins, J. Stieglitz, M. Gurven, H. Kaplan, and H. Allayee. 2011. Inflammatory gene variants in the Tsimane, an indigenous Bolivian population with a high inflammatory load. *Biodemography and Social Biology* 73:33–52.
Verghese, P. B., J. M. Castellano, and D. M. Holtzman. 2011. Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurology* 10:241–52.

Vitek, M. P., C. M. Brown, and C. A. Colton. 2009. APOE genotype-specific differences in the innate immune response. *Neurobiology of Aging* 30:1350–60.
Voelker, R. 2011. Stroke increase reported in HIV patients. *Journal of the American Medical Association* 305:552.
Vrba, E. 1995. The fossil record of African antelopes (Mammalia, Bovidae) in relation to human evolution and paleoclimate. In *Paleoclimate and Evolution with Emphasis on Human Origins*, ed. E. Vrba, G. Denton, L. Burckle, and T. Partridge, 385–424. New Haven: Yale University Press.
Wagner, A. 2007. Rapid detection of positive selection in genes and genomes through variation clusters. *Genetics* 176:2451–63.
Wang, C., W. A. Wilson, S. D. Moore, B. E. Mace, N. Maeda, D. E. Schmechel, and P. M. Sullivan. 2005. Human apoE4-targeted replacement mice display synaptic deficits in the absence of neuropathology. *Neurobiology of Disease* 18:390–98.
Watts, D. P. 2008. Scavenging by chimpanzees at Ngogo and the relevance of chimpanzee scavenging to early hominin behavioral ecology. *Journal of Human Evolution* 54:125–33.
White, T. D., B. Asfaw, Y. Beyene, Y. Haile-Selassie, C. O. Lovejoy, G. Suwa, and G. WoldeGabriel. 2009. Ardipithecus ramidus and the paleobiology of early hominids. *Science* 326:75–86.
WHO. 2009. World Population Monitoring. Focusing on Population Distribution, Urbanization, Internal Migration, and Development. A Concise Report. United Nations, Dept. Economic and Social Affairs. ST/ESA/Series A/284.
Wood, B., and N. Lonergan. 2008. The hominin fossil record: Taxa, grades and clades. *Journal of Anatomy* 212:354–76.
Wozniak, M. A., R. F. Itzhaki, E. B. Faragher, M. W. James, S. D. Ryder, and W. L. Irving. 2002. Apolipoprotein E-epsilon 4 protects against severe liver disease caused by hepatitis C virus. *Hepatology* 36:456–63.
Zhang, H., H. Liu, K. J. Davies, C. Sioutas, C. E. Finch, T. E. Morgan, H. J. Forman. 2012. Nrf2-regulated phase II enzymes are induced by chronic ambient nanoparticle exposure in young mice with age-related impairments. *Free Radicals in Biology and Medicine*: in press.
Zhou, W., D. Xu, X. Peng, Q. Zhang, J. Jia, and K. A. Crutcher. 2008. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *Journal of Neurotrauma* 25:279–90.
Zhu, Y., E. Nwabuisi-Heath, S. B. Dumanis, L. Tai, C. Yu, G. W. Rebeck, and M. J. LaDu. 2012. ApoE genotype alters glial-mediated neuroinflammation and synaptotoxicity in mice. *Glia* 60:559–69.
Ziba, C., L. Slutsker, L. Chitsulo, and R. W. Steketee. 1994. Use of malaria prevention measures in Malawian households. *Annals of Tropical Medicine Parasitology* 45:70–73.
Zink, A., U. Reischl, H. Wolf, and N. G. Nerlich. 2000. Molecular evidence of bacteremia by gastrointestinal pathogenic bacteria in an infant mummy from ancient Egypt. *Archives of Pathology and Laboratory Medicine* 124:1614–18.