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Aging, Life History, and Human Evolution

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Abstract

Aging occurs in all sexually reproducing organisms. That is, physical degradation over time occurs from conception until death. While the life span of a species is often viewed as a benchmark of aging, the pace and intensity of physical degradation over time varies owing to environmental influences, genetics, allocation of energetic investment, and phylogenetic history. Significant variation in aging within mammals, primates, and great apes, including humans, is therefore common across species. The evolution of aging in the hominin lineage is poorly known; however, clues can be derived from the fossil record. Ongoing advances continue to shed light on the interactions between life-history variables such as reproductive effort and aging. This review presents our current understanding of the evolution of aging in humans, drawing on population variation, comparative research, trade-offs, and sex differences, as well as tissue-specific patterns of physical degradation. Implications for contemporary health challenges and the future of human evolutionary anthropology research are also discussed.

INTRODUCTION

Anthropology has long addressed the subject of how aging has shaped the human condition. The question of how human culture and natural selection have shaped human aging as well as our response to the evolution of aging continues to merit attention. The evolutionary biology of aging has received increasing attention since it was established that the rate and intensity of physiological changes over time are influenced by natural selection (Rose 1991), with variation in age-related degradation of physiological function being proposed to emerge from the impact of metabolic costs, reproductive effort, environmental factors, genetics, and phylogeny. The evolution of aging in humans has raised several key questions, including determination of the roles of extrinsic and intrinsic mortality (internal and external causes), how contemporary humans compare to our hominin ancestors, and why humans exhibit such a long period of postreproductive life. Addressing these questions requires (*a*) testable hypotheses, (*b*) a deep understanding of human social and biological variation across ecologies, and (*c*) comparative research to assess differences from and commonalities with other species.

Humans live about as long as what would be predicted for our body size and metabolism. Many other factors suggest caution in using these basic life-history traits to predict life span, including the utility of life span itself as a metric of aging (Speakman 2005); life span here is defined as "the period of life from birth until death" (Bonsall 2006, p. 120). In more stochastic environments, life span is often compromised by hazards such as predators and climate extremes. While life expectancy varies among populations and has increased in many Western industrialized societies over the past century (Bongaarts 2005, Crimmins 2015), the U-shaped pattern of overall mortality risk across the entire life span is consistently similar across human populations, other primate species, and many other mammals (Caughley 1966, Chu et al. 2008, Finch 1990, Gage 1998). What this finding suggests is that physiological changes in aging are subject to natural selection and that species, specifically within primates and great apes, share similar constraints and selection pressures that result in common physiological changes with age. Moreover, physiological changes with age are often not uniform across organs and tissues. For example, ovarian follicle depletion during menopause in humans reflects a differential decline in reproductive function that precedes age-related reductions in other somatic functions (Austad 1994, Finch 2014). While most organs and tissues continue to mend themselves at older ages, other aspects of physiology such as immune and neurological function along with genetic and epigenetic challenges often reveal differential somatic changes with aging (López-Otín et al. 2013, Sadighi Akha 2018, Stegeman & Weake 2017).

Drawing on these collective insights, this review investigates our current understanding for how humans evolved their pattern of aging and how this pattern contrasts with that of other primate and mammalian species. Emerging evidence from the archaeological and fossil records will further inform physical evidence for sources of change in the evolutionary biology of aging within the hominin and anthropoid lineages. Finally, future directions for research are suggested.

Defining Aging

Evolutionary biologists, demographers, and physiologists discriminate between the definitions of aging and senescence in various ways. Cellular and evolutionary biologists view aging as a decline in function that occurs heterogeneously across various tissues and organs over time, whereas senescence is a cellular response that limits the proliferation of aged or damaged cells (McHugh & Gil 2018). Evolutionary demographers and biologists, however, commonly define senescence as age-associated increases in mortality and decreases in fertility. Environmental and other challenges contribute to variation in the intensity and pace of aging. In this review, we use the term

aging for the sake of consistency and clarity to describe age-dependent mortality and physiological deterioration over time.

Theories of Aging

Evolutionary theory provides a scientific approach that produces testable hypotheses about sources of variation in aging both within and between species. Moreover, natural selection is central to the evolution of traits that underlie the biology of aging (Rose 1991). In addition, life-history theory provides tools that interrogate the evolutionary associations between physiological demands that are often subject to the allocation of limited resources, such as physiology that is devoted to maintenance and that which is associated with reproduction. Life-history theory also identifies and examines the fitness implications of variation in traits that are common to all organisms, including aging (Ellison 2014, Stearns 1989). Life-history theory predicts that physical degradation is influenced by trade-offs between these and other demands, most prominently, the costs associated with reproduction. In addition, environmental factors, including those that are socially mediated such as paternal care, may affect the timing and investment of reproductive effort, thereby contributing to variation in aging. Extrinsic factors, such as environmental and social hazards, inform life-history decisions that affect reproduction and risk assessment, as well as decisions that influence health and well-being (Amir et al. 2016).

Primary theories that have guided aging research include pleiotropy, which is the accumulation of genetic mutations that contribute to not only the degradation of tissues and organs over time, but also the ability of individuals to repair age-associated damage (Medawar 1952). However, the question arises that if natural selection is able to favor individuals who are more adept at repairing age-related damage, why has natural selection not eliminated age-associated damage and mortality? Single-celled organisms that reproduce asexually appear to be immune from aging, hence the existence of immortal cell lines. However, the challenge with such organisms is distinguishing between individual daughter cells, which is essential for quantifying aging. Therefore, the process of aging is more relevant to multicellular organisms that reproduce sexually. Certain exceptions include the hydra (Hydra species), a multicellular jellyfish-type organism that under laboratory conditions does not exhibit age-related declines in physiological function or increases in age-related mortality, perhaps owing to the proliferation of stem cells that support hyperefficient cellular and tissue repair (Danko et al. 2015).

Antagonistic pleiotropy suggests that aging is affected by the decrease in the strength of selection with age and declines in fertility. Traits and genes that might be beneficial for fitness earlier in life might result in detrimental costs to survivorship at later ages when fitness is low and the influence of selection is less impactful (Williams 1957). The increased risk of reproductive cancers at older ages has been proposed to be an example of this source of morbidity and mortality (Eaton et al. 1994, Stearns & Koella 2008).

The rate of living hypothesis is based on the association observed between body size, metabolic rates, and life span. Larger organisms, particularly mammals, tend to have slower basal metabolic rates (BMR) and longer life spans. The primary underlying cause of life span variation is the difference in BMR in association with body size. In essence, smaller organisms have higher metabolic rates owing to the high surface-to-volume ratio that results in greater heat loss (Genoud 2002). Higher metabolisms in smaller mammals promote more tissue and cellular damage owing to greater oxidative stress (Pearl 1928). However, there are important exceptions to this association, which increase the likelihood that other factors contribute to life span (Austad & Fischer 1991, Munshi-South & Wilkinson 2010). Significant variation in metabolisms is also evident between great apes independent of body size (Pontzer et al. 2010), as well as between and within human populations (Levy et al. 2013, Pontzer et al. 2012, Snodgrass et al. 2005). Identifying sources of

variation in metabolic costs across the life span is key to understanding contributory interactions with aging.

Finally, the disposable soma hypothesis suggests that aging is significantly influenced by trade-offs among investment in reproduction, growth, and maintenance. In essence, increased investment in reproductive effort tends to result in fewer resources being devoted to maintenance in the form of cellular and tissue repair (Kirkwood & Austad 2000, Kirkwood & Rose 1991, Westendorp & Kirkwood 1998). Each of these theories provides specific insights to evolutionary aging.

PHYLOGENETIC INFLUENCES ON AGING

Phylogenetic associations are biological commonalities between species due to shared evolutionary ancestry such as egg laying between birds and reptiles. Along with other life-history traits, phylogenetic influences are important constraints on the biology of aging. For example, how organisms harvest and allocate metabolic energy is an important source of variation in the biology of aging. Ectotherms, organisms that depend on ambient temperature, have different constraints and physiological challenges compared with endotherms, species that generate their own body heat. As primates, humans share similarities owing to common ancestry with monkeys, great apes, and other mammals. Many of these similarities emerge from the early evolution of endothermy in mammals and other vertebrates (Legendre & Davesne 2020), although primates exhibit even slower aging compared with other mammals (Austad 1997, Austad & Fischer 1992, Jones 2011). Similarly, among endotherms, significant variation in aging exists, for example, in birds (Ricklefs 2010). These phylogenetic influences suggest that various orders share consistent traits related to aging as a result of common ancestry. Other organisms such as fish can exhibit extreme longevity as is the case of the Greenland shark (*Somniosus microcephalus*), which is among the longest-living vertebrates, with ages up to 272 years (Nielsen et al. 2016). The slower aging and long life spans of these vertebrates are likely related to ectothermy and other different forms of metabolism (Grigg et al. 2004, van de Pol et al. 2017). The aging physiology of humans and other primates, as endotherms, is influenced by our metabolic processes, such as the production of oxidative stress resulting from aerobic metabolism (Finkel & Holbrook 2000).

AGING AND REPRODUCTIVE EFFORT

Reproductive effort is the amount of time and energy that is invested in physiology and behavior that directly increase reproductive output, usually at the expense of other physiological demands such as those associated with growth and/or maintenance (i.e., immunocompetence) (Burger et al. 2010, Clutton-Brock 1984, Ellison 2003). Examples of reproductive effort include energy invested in reproductive tissues such as ovaries, testes, placenta, breast tissue, and fetal growth (Ellison 2003). In males, reproductive effort is also evident in sexually dimorphic tissue that augments competitiveness and attractiveness, commonly at the expense of morbidity and mortality (Bribiescas 2001, Bribiescas et al. 2012, Ellison 2003). Investment in reproductive effort therefore often results in increases in morbidity and mortality (Oakwood et al. 2001, Ziomkiewicz et al. 2016). Behaviors such as mate guarding and parental care are also examples of reproductive effort.

Associations between aging, metabolism, and reproductive effort have been suggested to be important sources of variation in life span (Kirkwood & Rose 1991, Westendorp & Kirkwood 1998). Demographic evidence intimates a trade-off between reproduction and life span in humans. For example, gravidity (the number of lifetime pregnancies) has been negatively associated with life span in rural Polish women; each additional pregnancy has been associated with about an 18-month decrease in postmenopausal life span. Number of children fathered had a differential

effect on paternal life span depending on the sex of the offspring. More sons had no effect on paternal life span while daughters had a positive effect, illustrating the important interface between biology and culture (Jasienska et al. 2006). Among preindustrial Finnish mothers (Helle et al. 2002) as well as historically recent Sami mothers (Helle et al. 2010), the number of sons was associated with compromised life spans. Although debate continues about the association between number of children and maternal life span (Cesarini et al. 2009, 2007), maternal energetic condition may be contributing to variation in this association between reproduction and aging (Jasienska et al. 2006).

Evidence of physiological mechanisms that contribute to this association is scarce in humans despite extensive research in nonhuman animal models (Harshman & Zera 2007, Reznick 1985). Hypothesized contributory mechanisms include oxidative stress (the production of toxic by-products during aerobic metabolism) and telomere shortening (a form of genetic degradation from mitosis). In addition, epigenetic aging, which results from methylation at a species-specific subset of cytosine–guanine base pairs, is significantly associated with chronological age. Accelerated epigenetic aging relative to chronological age is linked to increased risks for morbidity and mortality (Horvath & Raj 2018). These physiological processes have contributed to accelerated aging in conjunction with increased reproductive effort in humans and nonhuman animal models (Georgiev et al. 2015, Meer et al. 2018, Steinert et al. 2002). The pace and intensity of aging are influenced by reproductive effort, specifically metabolic investment in gestation as well as sexually dimorphic tissue in males (Adelman et al. 1988; Agarwal et al. 2005; Alonso-Alvarez et al. 2004, 2007). Biomarkers of oxidative stress in humans are positively associated with gravidity in rural Polish women (Ziomkiewicz et al. 2016). This effect appears to be mitigated by ecological context (Ziomkiewicz et al. 2018). Additional evidence indicates that gestation may contribute to accelerated telomere shortening and epigenetic aging, which may contribute to compromised genetic function (Ryan et al. 2018).

Humans and other primates are iteroparous, that is, they engage in multiple bouts of reproduction throughout their life span. This practice contrasts with other organisms, including mammals who engage in intense single bouts of reproduction (Oakwood et al. 2001, Rantes et al. 2002). Iteroparity allows organisms to allocate energy and effort across reproductive bouts, thereby spreading out the costs of reproduction and allowing more efficient allocation of energy toward maintenance, as is the case with primates. Semelparous organisms such as salmon and, in mammals, quolls often exhibit much shorter life spans that are associated with the intensity of energetic investment in a single bout of reproduction.

In human females, variation in energy availability between bouts of reproduction results in distinct patterns of caloric allocation. When energy availability varies, excess calories are often allocated to maternal somatic condition instead of to fetal tissue (Prentice & Goldberg 2000). This reallocation of energy is believed to contribute not only to greater fertility and additional bouts of reproduction, but also to maintenance, which can contribute to the slow rate of aging that is evident in primates, especially in humans.

AGING IN HOMININS

When the current pace and pattern of aging evolved in the hominin lineage is unclear. Most organisms exhibit the greatest mortality early and late in life, suggesting commonalities that are rooted in biophysics and phylogeny. Nonetheless, inferences from our last common ancestor, which is likely to be more similar to common chimpanzees (Brunet et al. 2002), intimate that life span in hominins before the emergence of the genus *Homo* about two million years ago was probably more similar to that of contemporary nonhuman great apes. The evolution of our genus resulted in the emergence of life-history traits that began to align with the current patterns of aging indicative of

Homo sapiens, although emerging evidence from other species of *Homo* reflect potential variation within our genus. For example, pelvic fossils of early *Homo* suggest that fetal growth patterns were similar to those in modern human life histories (Simpson et al. 2008), whereas tooth eruption patterns in Neanderthals suggest a faster growth rate, earlier maturation (Dean et al. 1986, Smith et al. 2007), and possibly shorter life span since "fast" life histories are usually associated with earlier age-related mortality. [See also Guatelli-Steinberg (2009) for a more detailed discussion of tooth eruption patterns in Neanderthals as well as Dean & Cole (2013) on the implications of tooth eruption and root growth during childhood and the evolution of life histories in the genus *Homo*.] Information on Denisovans is unavailable, although genetic markers associated with neurodegeneration are more aligned with *Homo* compared with *Pan* (McIntosh et al. 2012). Overall, the fossil record supports the idea that the contemporary pattern of human aging emerged recently during human evolution, almost certainly with the advent of modern *Homo sapiens* (Caspari & Lee 2004, Dean & Cole 2013).

The care and social integration of older individuals have been an ongoing debate among paleontologists and archaeologists despite the challenges posed by the taphonomy and representation of older individuals in the archaeological record (Appleby 2018, Welinder 2001). The discovery of older individuals with challenging physical injuries and disabilities in the archaeological record suggests that life span could have been augmented by the care and attention of others in the social group (Oxenham et al. 2009, Spikins et al. 2018, Tilley & Oxenham 2011). This finding is somewhat speculative, but comparative observations support this interpretation. Younger, disabled chimpanzees in the wild have been observed to be cared for by their mothers and siblings (Matsumoto et al. 2016); however, similar forms of care have not been observed for older individuals in chimpanzees or in any other great apes.

SOCIAL AND ENVIRONMENTAL INFLUENCES ON AGING

Humans are intensely social mammals. Therefore, stresses resulting from conspecific interactions are likely to influence health outcomes and well-being, including physiology that affects the intensity of age-related degradation. Accumulating evidence suggests that social and environmental factors influence the rate of age-related degradation in humans (Rentscher et al. 2020). Because social injustice often results in health inequalities and disparities between different groups, differences in aging physiology are likely to be distributed nonrandomly among various communities, including those that are marginalized owing to ethnic, racial, class, gender, or economic differences.

Contemporary reflections of the effects of social stress on aging are evident in racial/ethnic disparities in health challenges, particularly those that result in changes in biomarker association with aging. Geronimus (1992) noted the term "weathering" to describe the potential effects of social disparities on differences in health outcomes, specifically those related to aging and racism. Biological evidence for accelerated aging in association with social disparities has grown in tandem with technologies that quantify the specific physiological effects of aging. For example, experiences of racism by African Americans are associated with differences in telomere length, which is linked to accelerated aging, morbidity, and shorter life spans (Rej et al. 2020).

HUMAN ECOLOGICAL VARIATION

As a species, humans exhibit significant variation in sources of mortality with concomitant differences in social perceptions of aging. Demographic information from hunter-gatherer and other societies that rely on subsistence lifestyles suggests that life expectancy and intrinsic sources of mortality are comparable between populations and most primates (Bronikowski et al. 2011, Hill et al. 2001). That is, humans and nonhuman primates exhibit mortality patterns that are high

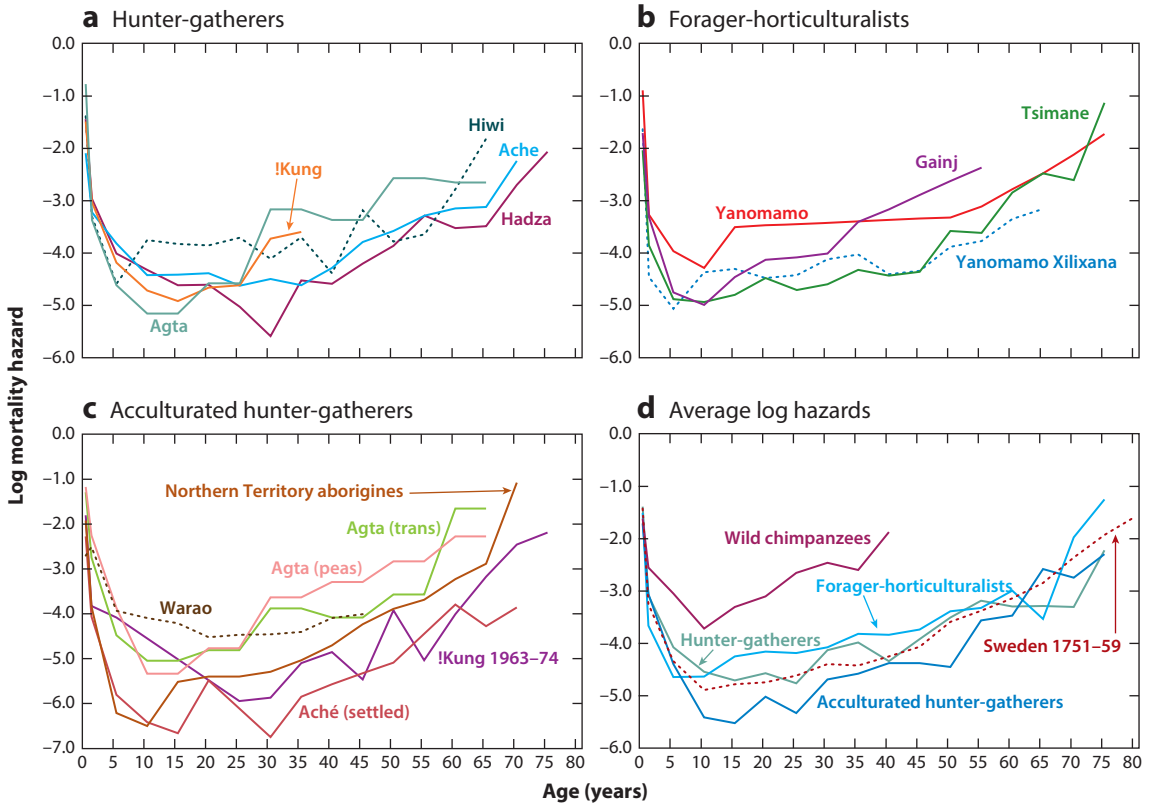

Figure 1

Mortality with age across several human populations and chimpanzees. Note that there is age-dependent variation in mortality between populations; the overall shape with higher mortality at younger and older ages is a shared characteristic. In addition, except for chimpanzees, maximum life span tends to converge on the sixth and seventh decade of life in all populations. Abbreviations: PEAS, peasant; TRANS, transitional. Figure adapted with permission from Gurven & Kaplan (2007).

during infancy, decline rapidly during childhood, remain constant across adolescence and early adulthood, and increase rapidly after the fourth decade of life (**Figure 1**). An increase in male mortality is also common across populations during early adulthood (Goldstein 2011). This U-shaped mortality curve does vary in association with extrinsic mortality, including variation in environmental sources of mortality such as disease, nutritional status, and violence. The shape of this mortality curve, as well as the long period of postreproductive life, informs our understanding of human characteristics that may have augmented life span such as sociality, tool use, and the procurement of consistent, high-quality food resources. Long-term demographic data from forager populations suggest that life span is positively affected by transitions to market economies, although the overall pattern of mortality is invariant (Gurven et al. 2007, Gurven & Kaplan 2007, Hill et al. 2007, Hill & Hurtado 1996).

Sex and Gender Variation

Women tend to have longer life spans compared with men. However, it is vital to note that aging variation associated with chromosome-defined sex is distinct from that associated with gender identity. Research on aging variation in the transgender and nonbinary communities is sparse but

growing (Ansara 2015, Fredriksen Goldsen et al. 2019). Those who are genetically male tend to have shorter life spans compared with females across virtually all populations (Case & Paxson 2005, Wang et al. 2016). The reason for this consistent difference is unclear, but several hypotheses suggest genetic, metabolic, and hormonal differences between sexes are contributory (Austad 2006, Bribiescas 2016). The lack of a second X chromosome in males has been suggested to allow the expression of deleterious genes that otherwise would be masked by the second X chromosome present in females; evidence for this cause remains under debate (Maklakov & Lummaa 2013). Higher BMR in males has been associated with decreases in life span (Ruggiero et al. 2008), although the contribution of BMR variation to aging continues to be debated (Speakman et al. 2002). Hormonal contributions to sex differences in life span remain unresolved. Comparisons of life spans in castrated men have yielded mixed results (Min et al. 2012, Nieschlag et al. 1993, Wilson & Roehrborn 1999).

Nonbinary gender identities are common across human populations. Communities composed of those with nonbinary gender identities are vibrant members of various societies and crucial to understanding the depth and complexity of the human condition. Gerontology of LGBTQ (lesbian, gay, bisexual, transgender, queer/questioning) communities has received only marginal attention (Fredriksen-Goldsen et al. 2013, 2014), with virtually no research being conducted outside of Western industrialized populations. Available research suggests that stress and negative health outcomes resulting from historical societal marginalization may have a negative effect on life spans among homosexuals (Cameron et al. 1998, Frisch & Bronnum-Hansen 2009).

Reproductive Senescence

Reproductive senescence (decreases in fertility with age) is of vital interest and importance in evolutionary biology and life-history theory owing to the central role of reproduction in evolution by natural selection. In humans, the effects of and association between aging and reproduction have garnered significant attention, owing primarily to the unusual pattern of extended postreproductive life span in women. Menopause is the cessation of fertility in females. Many mammals exhibit menopause, although humans, elephants, and some whales have been observed to have significantly extended life spans after their last reproduction (Cohen 2004, Croft et al. 2017, Erwin & Hof 2008). The definition of menopause in humans is one year since last birth or menstrual period. Changes in reproductive hormones also indicate the onset of menopause such as decreases in estradiol and increases in gonadotropins such as luteinizing hormone (LH) and follicle stimulating hormone (FSH). The gold standard of menopausal definition is follicle depletion. The quantification of follicle depletion is challenging, although measurements of anti-Müllerian hormone (AMH) have been associated with follicle depletion; that said, the association exhibits considerable variation (Andersen et al. 2015, Kelsey et al. 2011).

Other species such as whales and elephants exhibit a prolonged period of postreproductive life span compared with other mammals (Croft et al. 2017, Lahdenperä et al. 2014, Lee et al. 2016). However, humans are unique in this respect compared with other great apes and primates. Several hypotheses have emerged that engage this question. The grandmother hypothesis suggests that the indirect fitness benefits of grandmothers on the survivorship of grandchildren is a causal factor (Hawkes et al. 1998, Lahdenperä et al. 2004). Others suggest that extended life span and fertility at older ages select for longevity genes that are passed to both sons and daughters (Marlowe 2000). [See also Tuljapurkar et al. (2007) for a discussion about the prevalence of male fertility after the age of 50 across human populations and its potential contribution to the evolution of female postreproductive life span.] While debate continues about the evolution of human female reproductive senescence (menopause), that follicle depletion is the physiological

cause of the acute decline in fertility in women around the age of 50 is well established (Gosden & Faddy 1994, Richardson et al. 1987). The primary question that therefore emerges is how extended postreproductive life span evolved in humans compared with other mammals (Austad 1994, Finch 2014).

Reproductive senescence in males has received considerably less research attention. A primary challenge is the inability to assess male fertility with the same precision as females. Recent assessments of foraging and non-Western populations suggest that, similar to women, men exhibit a significant postreproductive life span (Vinicius et al. 2014) and continue to father children after the age of 50 (Tuljapurkar et al. 2007). While fertility in men declines with age, there is no absolute precipitous decline in the ability to reproduce as is the case with menopause. Reproductive hormone levels in men do exhibit changes with age; however, there is a significant range of variation in Western industrialized men. As part of the Baltimore Men's Study, Harman and colleagues (2001) reported arguably the most comprehensive longitudinal study of testosterone and sex hormone binding globulin (SHBG) in men. Both total and free testosterone levels exhibit a modest decline with age; however, a tremendous amount of variation in age-related declines is evident (Harman et al. 2001).

Reproductive senescence in non-Western, nonindustrialized male populations is somewhat scarce. Changes in testosterone and other reproductive hormones vary between populations. Although testosterone exhibits a decline in Western men, others demonstrate a more attenuated decline, and in hunter-gatherers, evidence shows virtually no change with age (Ellison et al. 2002, Uchida et al. 2006). Among Aché men of Paraguay, there is no change in testosterone with age, although gonadotropins such as LH and FSH exhibit an increase with age; this increase is commonly observed in Western populations (Bribiescas 1996, 2005). Short-term testosterone increases with acute effort such as wood chopping is evident in older Tsimané men (Trumble et al. 2013), which is consistent with evidence in other clinical literature (Baker et al. 2006); this finding suggests that responsiveness of the hypothalamic-pituitary-testicular hormone axis to acute activity in older men is a common trait independent of lifestyle or ecology.

Neurodegeneration

Humans, nonhuman primates, and other long-lived mammals such as cetaceans invest a significant amount of energy and growth/development time to brain tissue, with about 20% of BMR allocated to the brain in humans and with metabolic investment peaking at childhood (Kinney & Tucker 1992, Kuzawa et al. 2014). The selection pressures that have led to the evolution of a metabolically expensive organ that allows greater behavioral plasticity but also demands high oxygen levels and caloric stability also likely create other costs (DeWitt et al. 1998, Sherwood & Gómez-Robles 2017). The effects of aging on the brain are therefore of high importance to survivorship and fitness in humans, given the significant amount of life after peak fertility in males and females. Neural degeneration is an especially challenging problem because neural cells do not commonly regenerate or recover quickly from damage.

Cognitive decline with age is consistently more prominent in human males compared with females. While older males perform well on some tasks such as visuospatial ability, similar-aged females outperform males on most other cognitive tasks (McCarrey et al. 2016), although a recent systematic review reports that sex differences in cognitive decline do not emerge until after the age of 80 (Ferreira et al. 2014). Alzheimer's disease (AD) is arguably the most common expression of neurological degeneration with age. The wide range of heterogeneity that results in different forms of cellular degeneration and expression creates research and clinical challenges in addressing AD. Differences in risk and expression of AD between males and females are among the most

common forms of heterogeneity. A recent review summarizes the contemporary questions of sex variation in AD. Variance in risk of expression of AD is evident; women commonly demonstrate faster cognitive decline after diagnosis and more rapid brain atrophy (Ferretti et al. 2018).

Outside of Western, industrialized populations, very little is known about conditions that are often associated with aging, such as AD, Parkinson's disease, or other forms of dementia (Poveda 2003). Attempts to quantify the contribution of cultural variation to AD diagnosis tests have met with some success but have been limited in scope (Della Sala et al. 2018). In a study of the interactions between testosterone supplementation, oxidative stress, and AD risk in Mexican American and white men, Mexican Americans appeared to be protected from the negative effects of testosterone supplementation, possibly as the result of greater endogenous antioxidant defenses (Cunningham et al. 2014).

Evolutionary approaches to understanding AD have highlighted the importance of sleep (Nesse et al. 2017), exercise (Raichlen & Alexander 2017), reproduction, and comparative research (Bufill et al. 2013). Evidence on the presence of AD or similar conditions in other great apes is mixed. The apolipoprotein E (*APOE*) gene is associated with AD as well as with longevity in humans. *APOE* is polymorphic, with three alleles (E2, E3, E4) being evident in humans. The distribution and frequency of these alleles across human populations are quite diverse and not well understood, although the E4 variant is associated with a higher risk for AD and other diseases. Chimpanzees, however, are monomorphic. A genetic examination of captive chimpanzees (*Pan troglodytes verus*) and wild individuals (*Pan troglodytes schweinfurthii*) revealed monomorphism with only one unique allele. Bonobos (*Pan paniscus*) have the same monomorphism as chimpanzees. Neanderthals and Denisovans exhibited *APOE* polymorphisms that are similar to those of modern humans, with the E4 allele being functionally similar (McIntosh et al. 2012). Because chimpanzees commonly exhibit significantly more genetic variability compared with humans (Kaessmann et al. 2001), it is remarkable that they are monomorphic for this gene.

New pathways for understanding AD have recently been associated with the potential effects of antagonistic pleiotropy (Bufill & Blesa 2005). In particular, reproductive effort has emerged as a research covariable of interest. As summarized by Fox (2018), the following hypotheses have been proposed to explain the evolutionary underpinnings of AD:

- Novel extension of the life span, i.e., that before the advent of Western medicine, individuals did not live beyond the fifth decade of life;
- Age-related selection bias, i.e., that traits affecting younger individuals are more sensitive to selective pressure because they are more likely to influence reproductive success;
- Antagonistic pleiotropy (Williams 1957), i.e., that genes that are beneficial in one way or during certain phases of the life cycle may be detrimental in other ways or at other phases;
- AD is a by-product of rapid brain evolution;
- AD neuropathy is delayed in humans compared with ancestral species owing to selection for grandmothering;
- Novel alleles protective against AD were selected to delay disease onset;
- AD is a by-product of selection against cardiovascular disease; and
- AD is caused by a thrifty genotype (Neel 1962), i.e., the idea that sacrificing energetically costly traits is adaptive in conditions of caloric stress.

The examination of all these hypotheses is beyond the scope of this review. However, certain research directions merit attention. As with many health challenges, especially those that are associated with aging, antagonistic pleiotropy is a common source of age-related illness. Reproductive effort may exacerbate the contribution of antagonistic pleiotropy to AD risk. In women, number of children has been associated with AD risk (Beeri et al. 2009). The novel extension of life span is

unlikely because demographic evidence from contemporary hunter-gatherer populations as well as from the archaeological record suggests that life spans extending beyond the sixth decade of life have been common since the emergence of modern *Homo sapiens* over 200,000 years ago (Gurven & Kaplan 2007, Hill & Hurtado 1996, Lovejoy et al. 1977).

That the *APOE* E4 allele is present in modern humans, Denisovans, and Neanderthals but is relatively absent in chimpanzees suggests a novel emergence of genes associated with AD. Whether the emergence of this genetic difference was in conjunction with some other gene or a product of the evolution of a large brain compared with other great apes remains unclear. The lack of information on the *APOE* gene in other large-brained mammals such as elephants and whales adds to the lack of clarity. The immunomodulatory receptor Siglec-3 (CD33) is associated with late-onset AD. CD33 is the only Siglec that seems to have evolved convergently in toothed whales, another mammal with a prolonged postreproductive life span (Siddiqui et al. 2017). Proteins associated with AD have also been observed in some species of dolphin as well as in sea lions (Di Guardo 2018, Neely et al. 2015).

COMPARATIVE AGING

As an order compared with other mammals, primates exhibit life spans generally in alignment with expectations for their body size and metabolism (Austad 1997, Speakman 2005). The primary difference between primates and other mammals is that primates achieve larger body sizes by growing for longer periods of time as opposed to faster growth in other mammals (Stearns 1992). The evolutionary implications for this trait are that, as an order, primates have developed biological and behavioral strategies to decrease extrinsic mortality relative to other mammals, thereby allowing them to produce altricial offspring after some extended period of growth, in essence evolving a "slow" life-history regimen (Charnov & Berrigan 1993, Jones 2011). Nonetheless, the pattern and pace of mortality with age in most primate species are relatively invariant, suggesting that mortality pressures are common and shared by most primate species (Bronikowski et al. 2011) (**Figure 2**).

Among primates, prosimians such as sifakas and lemurs merit special attention because they exhibit exceptionally long lives for their body size. Sifakas and lemurs fall into the rare category of mammals who exhibit exceptionally long life spans for their body size. These include bats, naked mole rats, and some marsupials (Austad & Fischer 1991, 1992). By comparison, their lengthy life spans would be on par with a domestic house cat commonly living into its third decade. The reasons for extended longevity among lemurs and sifakas are unknown, although some data have suggested that the hypervariable environment and lack of predators on Madagascar may be contributory. That is, lemurs and sifakas exhibit a "bet hedging" life-history strategy that allows them to defer the costs of reproduction until environmental conditions are conducive to reproducing (Richard et al. 2002).

Although long-term field investigations of gorillas, orangutans, and bonobos that inform our understanding of aging in those species are scarce (Lowenstine et al. 2016), current knowledge based on data from multiple field sites of wild chimpanzees as well as captive communities suggests that chimpanzee life span is between 50 and 60 years, with considerable variation between wild and captive populations (Hill et al. 2001). However, recent studies have challenged this difference between humans and chimpanzees. Some wild chimpanzee communities may live about as long as some hunter-gatherer populations. The authors suggest that with favorable ecological conditions chimpanzee longevity can be significantly extended compared with previous reports (Wood et al. 2017) (**Figure 3**). The Ngogo and Kanyawara communities live in close proximity to each other, about a day's walk, within Kibale National Park in Eastern Uganda. The stark difference between

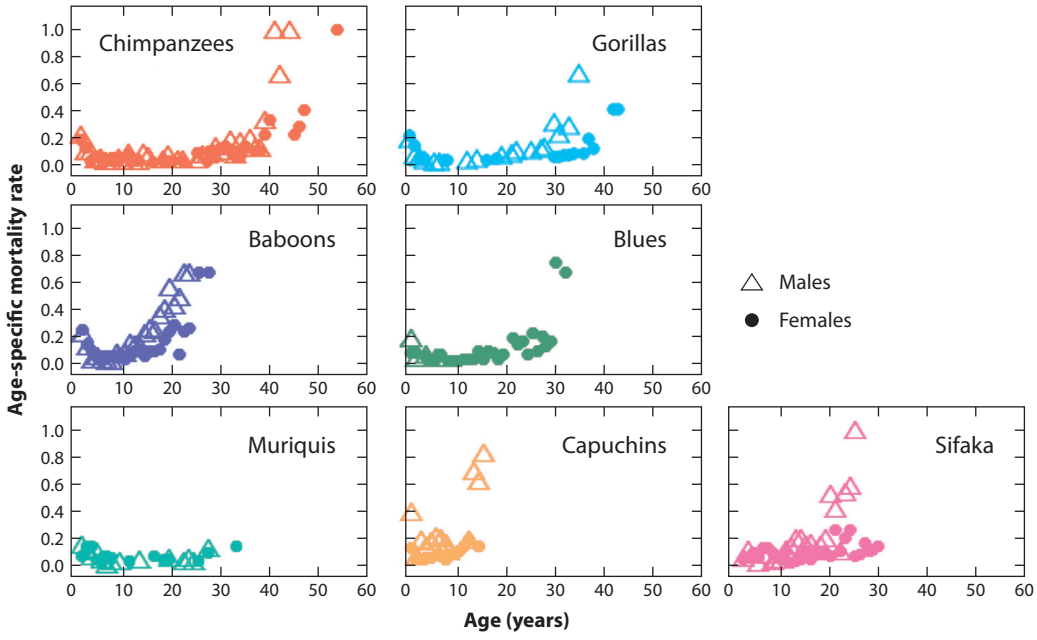

Figure 2

Age-specific mortality in representative primate species. Figure adapted with permission from Bronikowski et al. (2011).

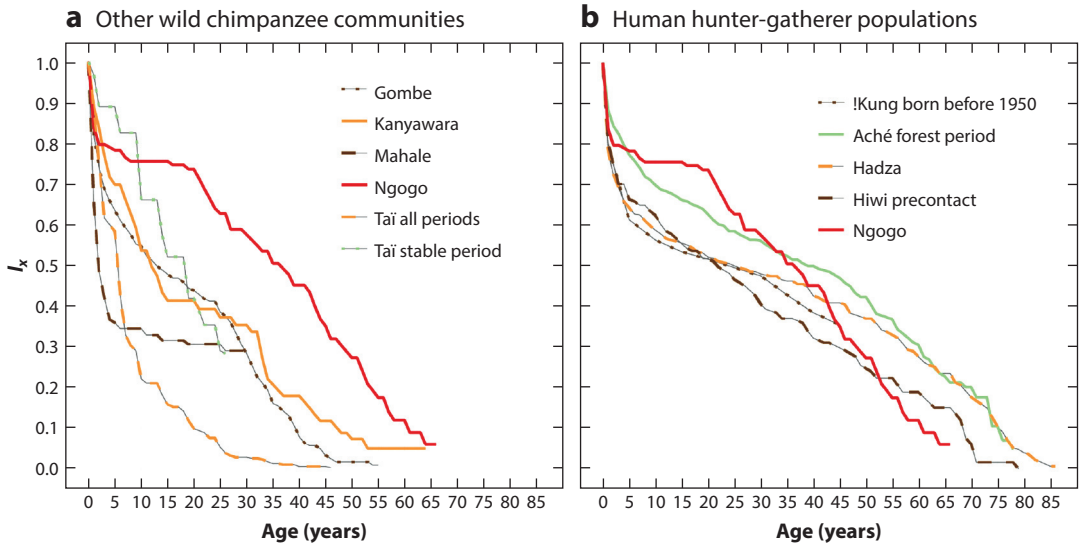

Figure 3

Survivorship at Ngogo for both sexes combined compared with that of (*a*) other wild chimpanzee communities and (*b*) human hunter-gatherer populations. Lines plot the values of l_x as reported in life tables. Data sources are as follows: Gombe (Bronikowski et al. 2016); Kanyawara (Muller & Wrangham 2014, table 1); Mahale (Nishida et al. 2003, table 3); Ngogo (Wood et al. 2017); Taï all periods (Hill et al. 2001); Taï stable period (Boesch & Boesch-Achermann 2000); Dobe !Kung (Howell 2010); Aché forest period (Hill & Hurtado 1996); Hadza (Blurton Jones 2016); Hiwi precontact (Hill et al. 2007). Figure adapted with permission from Wood et al. (2017).

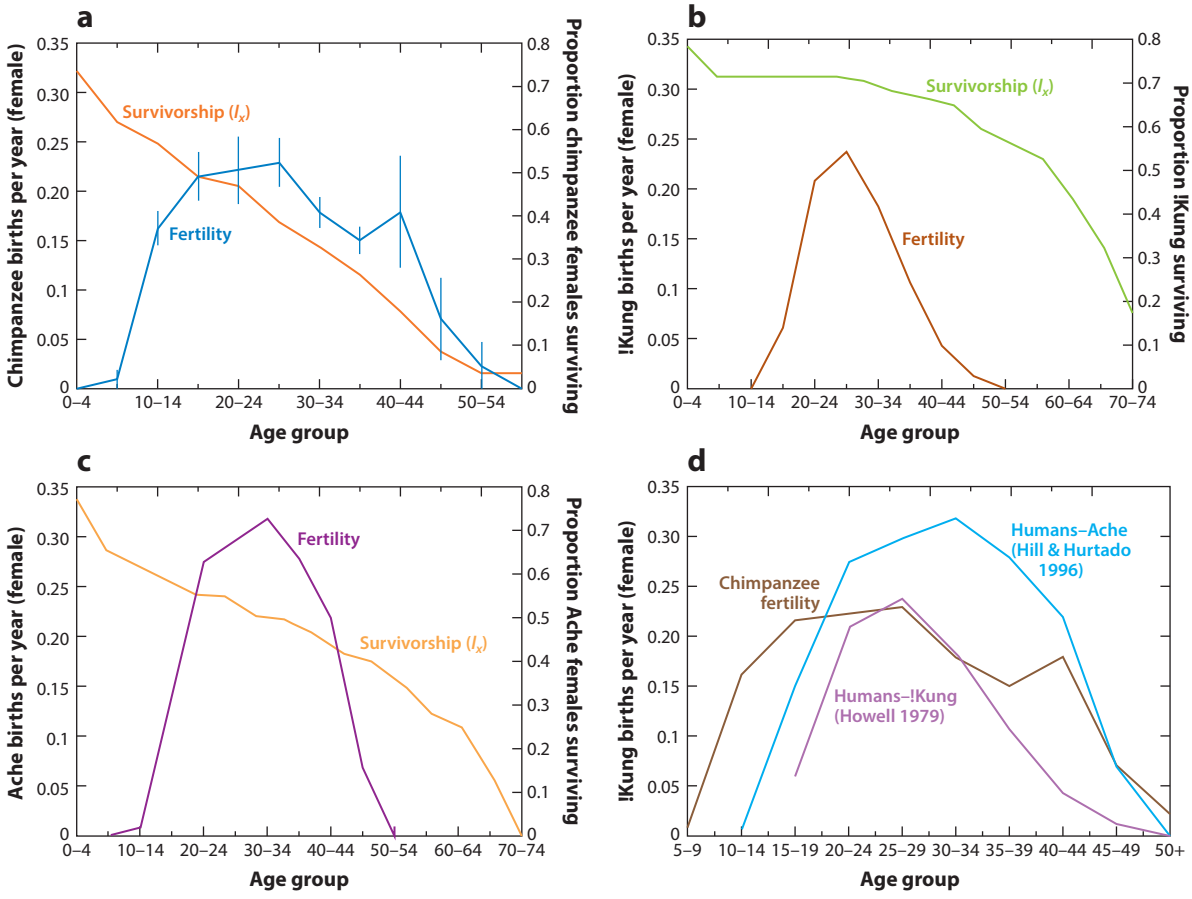

Figure 4

Comparison of chimpanzee and human age-specific fertility and mortality patterns. Figure adapted with permission from Emery Thompson et al. (2007).

these two groups is striking, suggesting that significant differences in age-related mortality can emerge even with local ecological variation.

Our understanding of reproductive senescence in great apes is incomplete. However, data from chimpanzees have also grown significantly over the past decade owing to long-term field studies and the postmortem examination of reproductive tissues in our closest living evolutionary relative, the chimpanzee. Reproductive endocrine studies show that chimpanzees in the wild exhibit signs of menopause around the age of 50, which aligns with the reproductive biology of humans (Emery Thompson et al. 2007). The overall pattern of reproductive senescence, or decline in fertility, is similar between humans and chimpanzees, although chimpanzees tend to start reproducing earlier (**Figure 4**).

Histological examinations of ovarian follicles in deceased captive chimpanzees contribute additional supportive evidence that follicle depletion (atresia), a major contributor to the onset of menopause, mirrors human patterns (Jones et al. 2007). In alignment with processes in humans, follicle depletion in chimpanzees accelerates in the third and fourth decades of life, with an abrupt and total depletion occurring around the age of 50. In sum, these data suggest that the pattern of

reproductive senescence is very conservative and likely shared with our hominin ancestors, possible as far back as the last common ancestor with chimpanzees, approximately 7 million years ago.

FUTURE DIRECTIONS

The engagement of evolutionary and life-history theory within medical research and treatment strategies has received significant attention (Nesse et al. 2010, Stearns & Koella 2008). However, biological evidence of the influence of specific life-history traits such as reproductive effort on aging, which may inform variation in health outcomes and population disparities in humans, remains sparse. While emerging evidence suggests that associations between life-history traits are likely to contribute to current health challenges, especially in underserved communities (Bribiescas & Ellison 2007, Ellison 2014, Taylor et al. 2013), there is considerable room for growth in the deployment of this perspective by the medical community. Social factors and the vibrant community of biocultural researchers who engage in applied anthropology also provide valuable insights that not only complement evolutionary perspectives but also provide important perspectives into social and political forces that impact dignified and healthy aging. The merging of clinical, evolutionary, social, and applied perspectives is likely to stoke bold new insights into our understanding about how all humans age.

The deployment of field-friendly and noninvasive assessments of biomarkers continues to hold promise and yield vital information. For example, biomarkers of oxidative stress are increasingly being deployed to explore variation in the physiology of aging in association with differences in human ecologies and between different primates (Georgiev et al. 2015; Ziomkiewicz et al. 2016, 2018). The significance of this information lies both in the basic science of aging and also in applied anthropology. For example, assessment of the effects of reproduction on longevity and morbidity in women demonstrates the importance of postnatal health education and resources (Ziomkiewicz et al. 2016, 2018). In many parts of the world, women with high fertility often suffer from the lack of reproductive health resources such as family planning and rights to govern their own reproductive lives. Anthropology is positioned to help address this issue through applied research and basic science.

Similarly for men, understanding the broad range of variation that is evident in hormone changes in association with age is vital for informing decisions on such issues as testosterone replacement therapy. The range of male-specific health issues that are associated with aging would also benefit from greater awareness of human variation. For example, prostate cancer and benign prostatic hyperplasia (BPH) are believed to be a common health issue in older men. However, recent evidence from non-Western, nonindustrialized societies has challenged this view, demonstrating that BPH is not an inevitable outcome of aging (Trumble et al. 2015); that said, other research reports high rates of prostate health issues that align with those in industrialized societies (Campbell 2005).

Broadening the scope of our understanding of human variation, both genetically and ecologically, is vital for a more complete understanding of aging. Moreover, comparative research into other long-lived species, both mammalian and nonmammalian, would be informative to determine commonalities that may have shaped the evolutionary biology of aging in all life forms, including humans.

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