Mutation accumulation in genes with sex-biased fitness effects: A parsimonious explanation for sex differences in lifespan and ageing

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Summary

Sex differences in lifespan and ageing pervade the tree of life, yet their evolutionary origin is still debated. Adaptive trade-off models have long dominated the field but show mixed empirical support. Here we argue that mutation accumulation in genes with sex-biased fitness effects is the most parsimonious evolutionary cause of sex-biased ageing. Because anisogamy and ecology shape reproductive and survival schedules, natural selection weakens faster in one sex than in the other. The sex with the fastest declines in selection gradients with age will accumulate a greater load of late-acting deleterious mutations, leading to faster ageing and shorter lifespans. Critically, this mechanism works without requiring sex-specific resource allocation or genetic trade-offs. Therefore, it can resolve previously puzzling and contradictory variation observed in experimental and comparative studies because its predictions are context-dependent according to prevailing demographic patterns. Because this model requires only sex-biased gene expression and differences in late-age reproductive contributions towards future generations, it is sufficient to explain sexual dimorphism in lifespan and ageing across organisms with different sex determination systems. We discuss existing empirical support for this new model and outline approaches to test its predictions and quantify the role of mutation accumulation in the evolution of sex differences in lifespan and ageing.

Introduction

Sex differences in lifespan and ageing are ubiquitous across taxa, yet whether this arises through adaptive trade-offs or other evolutionary processes remains unresolved. Males typically die sooner than females across diverse organisms. However, the magnitude of sex differences in lifespan varies widely, with some taxa showing reversed patterns or no lifespan differences at all. Phylogenetic comparative analyses suggest that context-dependent ecological and social factors can reverse or diminish the expected elevated mortality biases in males [1, 2]. These observations challenge the generality of evolutionary mechanisms that generate and maintain sex differences in lifespan and ageing.

Sex differences in lifespan have traditionally been explained by sex-specific adaptive life-history trade-offs: males, for example, are predicted to prioritise mating effort and sexual competition at the cost of somatic maintenance and long life, whereas females should invest more heavily in survival to support repeated reproductive events [2-8, but see 9]. Such sex-specific trade-offs align with a broader theory of antagonistic pleiotropy [10], which argues that genes conferring fitness advantages early in life may be favoured by selection even if they carry detrimental effects later in life. Thus, traits beneficial for early-life mating success in males might accelerate ageing if detrimental for late-life fitness, thereby generating sex differences in lifespan because of evolutionary pressures acting differently across sexes. Despite their intuitive appeal, however, these trade-off models have received mixed empirical support.

Recent comparative and experimental studies increasingly challenge the notion that sex differences in lifespan arise primarily from genetic and/or resource allocation trade-offs between reproduction and somatic maintenance. While greater male-biased mortality is common in polygynous mammals, its magnitude and direction vary, and it is not always explained by the strength of sexual selection alone [8, 11]. A recent comparative study in mammals found that both mating system and sexual size dimorphism, representing proxies for the strength of sexual selection, showed no detectable association with lifespan or ageing rate [8, 12]. Moreover, experimental manipulations in model organisms such as *Drosophila melanogaster* and *Caenorhabditis elegans* demonstrate that lifespan can be extended without costs to reproductive output when key genetic pathways such as insulin/IGF-1 signalling or TOR are modified in an age- or tissue-specific manner [13-21]. Similarly, experimental evolution studies suggest that links between long life and reduced reproduction can often be uncoupled [22-25]. Finally, a recent metanalysis of studies of natural populations of birds provides little evidence for reproduction-survival trade-offs and suggests that variation in reproduction within natural ranges results in negligible survival costs [26]. Together, these findings highlight a gap between classical trade-off models and observed patterns in both the laboratory and nature, suggesting that while life-history trade-offs may contribute to sex-biased ageing, additional evolutionary processes are likely required to fully explain sex differences in lifespan and ageing. This emerging view calls for a renewed emphasis on integrating classical evolutionary theory with empirical insights to explain when and why the sexes should differ in lifespan and rates of ageing.

We suggest that a complementary, and arguably more parsimonious, explanation for the evolution of sex differences in lifespan and ageing requires a focus on the consequences of sex differences in age-specific fertility. Anisogamy – the difference in gamete size that underpins the evolution of the sexes – results in the evolution of sex-specific life histories [27-31]. As a result, males and females often differ in the timing and rate of reproduction, meaning that the strength of natural selection on survival and late-life performance can decline at different rates in the two sexes. For instance, in some species, male-male competition results in a delayed onset of male relative to female reproduction, which necessarily results in selection gradients for survival declining later in life in males than in females [32]. Conversely, when males reproduce at high rate early in life, purifying selection to remove mutations that act late in life, or mutations whose deleterious effects are more pronounced in late life, will weaken more rapidly in males than in females which will show prolonged reproduction. This sex-specific decline in selection gradients predicts that mutation accumulation alone can generate intrinsic sex differences in ageing, without the requirement for reallocation of resources between different traits, or the existence of sex-specific genetic trade-offs between early-life and late-life performance.

This process requires only two minimal conditions to be met beyond the inevitable decline of selection with age proved by Hamilton [33]: (1) sex-and-age specific gene expression or mutational effects and (2) differing age-specific reproductive contributions to population growth between the sexes. When those requirements are satisfied, then sex differences in lifespan and ageing can evolve via mutation accumulation alone without trade-offs. Mutation accumulation is the parsimonious model because evolution results from selection acting directly on sex-and-age-specific genetic variances, whereas antagonistic pleiotropy (AP) requires an element of correlated selection acting indirectly across different ages. Therefore, AP represents a more restrictive genetic architecture. Trade-offs can play a role via AP, of course, but they are not a necessary requirement for sex differences in lifespan and ageing to evolve.

From this perspective, sex-specific ageing should be treated not as an outcome of optimised sex-specific allocation trade-offs but as the product of sex differences in the rate of change of selection, whenever such differences are present in the population. Recognising mutation accumulation as the more parsimonious explanation reframes long-standing debate about the origin of sex differences in lifespan. Importantly, it can also prompt new approaches and tools for empirical studies of the evolution of sex-specific life-histories. If demographic asymmetry is key, we should find that the sex with earlier onset of reproduction and/or higher rate of early-life reproduction will also carry a higher late-acting mutational burden.

This argument requires that sex-specific schedules of reproductive contributions generate variation in the declines of the strength of natural selection with age. In the following section, we extend Hamilton's [33] model to formalize this mechanism, showing how sex differences in age-specific vital rates create divergent trajectories of selection decline and enable sex-specific mutation accumulation. We discuss existing experimental studies that support this view and suggest future research directions, from identifying genomic signatures to experimental evolution, with the aim of disentangling adaptive and non-adaptive forces shaping sex differences in lifespan and ageing.

Hamiltonian forces of selection within each sex shaped by age-specific contributions towards future generations

Hamilton [33] demonstrated that the strength of natural selection against age-specific mortality must decline with age because selection is strongest when the greatest expectation of contribution towards the rate of population growth (i.e., realised reproduction) remains in the future. This insight provides the conceptual backbone for the evolutionary theory of ageing. However, Hamilton's formulation assumes sex-independent vital rates. When males and females of the same age differ in their expectation of future contributions to population growth, then the strength of selection will follow different age-specific trajectories in each sex. Here we extend Hamilton's framework to demonstrate how sex-specific vital rates generate divergent selection trajectories.

Hamilton [33] describes selection against age specific-mortality (or *for* the natural logarithm of age-specific survival, $P(x)$, in terms of sex-independent vital rates (1966). Expressed using a continuous-time formulation,

$$\frac{dr}{dln\big(P(x)\big)} = \frac{\int_x^\infty L(y)m(y)e^{-ry}}{\int_0^\infty yL(y)m(y)e^{-ry}} \qquad (1)$$

where $L(y)$ is the cumulative rate of survival from birth to *y*, $m(y)$ is the mean fertility of living individuals at age *y*, and *r* is Fisher's Malthusian rate of population growth. The last is defined in terms of the Euler-Lotka equation, $\int_0^\infty L(y)m(y)e^{-ry} = 1$; it can be seen from this that the population growth rate follows entirely from the set of vital rates. This expression assumes that populations are stable: they are free to increase or decrease in number, but their growth rates cannot change. The numerator of eq (1) defines the age-distribution of new parents; selection is seen to decline with age because the fraction of these parents that have experienced some age of interest *x* must decline as *x* increases. The denominator is the mean age of new parents, which is one definition of generation length. Thus, eq (1) expresses the strength of age-specific selection acting over one time interval.

One can decompose the numerator of eq (1) into sex-specific distributions of the ages of new parents. Sex-specific selection gradients follow from this. With 50/50 sex ratios at birth and the requirement that all individuals have exactly one father and one mother, then these follow from the age-distribution of the new parents of one specific sex,

$$\frac{dr}{dln\big(P(x,S)\big)} = \frac{1}{2}\frac{\int_x^\infty L(y,S)m(y,S)e^{-ry}}{\int_0^\infty yL(y)m(y)e^{-ry}} \qquad (2),$$

where *S* indicates that the survival or fertility rate is specific to the sex of interest. Note that whilst the vital rates can be sexually dimorphic, the intrinsic rate of growth for the male and female portions of the population are constrained to be identical. This implies between-sex regulation of vital rates, and the mechanisms of such feedback will likely be specific to the biology and ecology of the species.

Dimorphic selection will shape the evolution of age-specific survival, and thus actuarial senescence, according to the degree of selective differences and the nature of the correlations between the genetic determinants of survival in both sexes. If these correlations tend to be positive, then natural selection will act to minimize sex dimorphisms because sex-specific selection will work in concert on the same heritable factors. In the absence of such genetic correlations across the sexes, the evolution of lifespan is less constrained, and lifespan and/or ageing dimorphisms are expected to evolve in proportion to the differences in selection. In the presence of negative genetic correlations, we can expect that dimorphisms will evolve to be even stronger. In the proceeding sections we discuss empirical evidence for sex-specific genetic variation for lifespan.

In Figure 1, we used a hypothetical scenario which is loosely based on a large mammal species with high male-male competition for matings, such as Red Deer (cf. [34]). In this hypothetical population, males start to reproduce later than females, because young sexually mature males are largely excluded from reproduction by older dominant males. Dominant males have higher but shorter reproductive peak than females; it is higher because they control access to females and can fertilise many females during this period, while female fecundity remains stable, and it is shorter because male annual survival declines much faster than female annual survival owing to injuries sustained in male-male competition.

In line with eg (1) and eg (2) above, we assumed a stable but growing population (population growth rate $\lambda = 1.02$). We note, however, that the results are qualitatively similar for different population growth rates, including stationary populations (intrinsic rate of increase $r = 0$). We also assumed equal sex ratios at birth. We illustrate our point of how sex-specific differences in fertility schedules translate into sex-specific changes in selection gradients (Figure 1) by showing the progression from the vital rates (panel A) to selection gradients (panel C) using the probability distribution plot (panel B). We think this is a novel way of demonstrating the link between demography and age-specific selection.

We emphasise that this is an example, and sex-specific selection gradients will decline in different ways in different populations of sexually reproducing organisms. However, it illustrates our main point that sex-specific reproductive schedules are sufficient to result in sex differences in the decline of the strength of selection leading to sex-specific mutation load of deleterious alleles whose effects on fitness are primarily expressed in late life.

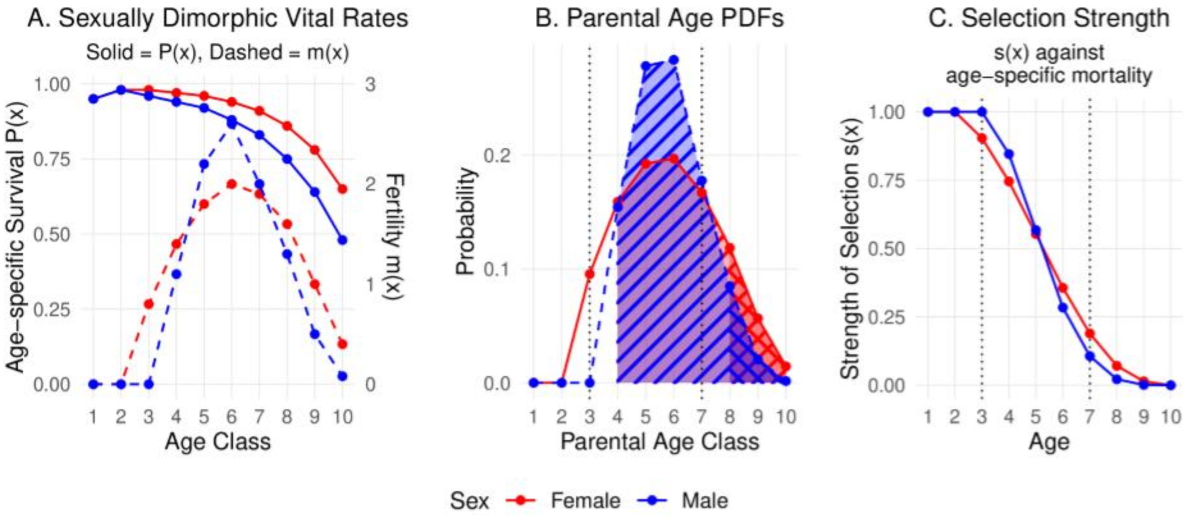

Figure 1. Sex-specific demography and age-specific selection for survival, illustrated using a discrete-time, post-breeding census model with annual age classes. (A) Sexually dimorphic vital rates showing age-specific survival P(x) (solid lines) and fertility m(x) (dashed lines) for females (red) and males (blue), representing a large mammalian species with pronounced intra-sexual competition in males. Male reproduction is delayed but reaches higher peak fertility, with steeper senescent decline in both survival and fertility. (B) Probability distributions (probability density functions, PDFs) of sex-specific parental age at birth. Vertical dotted lines at ages 3 and 7 mark example ages; hatched areas show reproductive contributions from age 4 onwards (diagonal) and age 8 onwards (cross-hatched), illustrating that these proportions differ between sexes. (C) Strength of selection s(x) against age-specific mortality equals the area under each parental age distribution from age *x* + 1 onwards. The hatched areas in panel B correspond directly to the strength of selection values in panel C. The faster decline in male selection results from compressed reproductive lifespan and higher adult mortality rates.

Sex-specific gene expression allows differential mutation accumulation

The model presented above shows that males and females experience different age-specific selection gradients when their contributions to future generations differ across ages. For these vital rates differences to lead to the evolution of sex-specific ageing, at least some genes affecting age-specific performance must have sex-specific effects on phenotypes. This requirement is met because sex-biased gene expression generates the genetic architecture necessary for mutation accumulation to evolve at sex-specific rates.

Because males and females share most of their genome, adaptive divergence between the sexes is expected to rely largely on sex-biased regulation of autosomal and X-linked genes. Comparative transcriptomic surveys demonstrate that more than 50% of the transcriptome can show sex-biased expression [35, 36], and that sex-biased genes evolve rapidly [37]. In humans, 37% of genes show sex differences in expression in at least one tissue [38], and 91.4% of FDA-approved drug target genes show sex difference in expression in at least one tissue [39]. Recent experimental study found that sex-specific selection leads to rapid evolution of sexually dimorphic transcriptomes [40].

Beyond sex-biased expression patterns, there is substantial sex-specific genetic variation for lifespan across taxa [41-43]. For example, a comprehensive study using hemiclonal analysis in *D. melanogaster* found that the heritability of lifespan is largely sex-limited and ~75% of additive genetic variation in lifespan and actuarial senescence is sex-specific [44]. This suggests that traits affecting lifespan and rates of ageing are relatively free to evolve independently in each sex. Consistent with this is the observation of ample autosomal and X-linked additive genetic variation for lifespan within each sex in *Drosophila* [45]. The extent of sex-specificity varies across taxa. In natural fertility humans, the cross-sex additive genetic correlation for late-life (post-50) lifespan is 0.817 [46], indicating substantial but incomplete genetic overlap between the sexes. A more recent study of genetics of longevity in heterogenous mice (*Mus musculus*) also identified sex- and age-dependent QTLs that affected sexes differently at different ages [47]. Such effects predispose populations to evolve sex differences in lifespan in response to sex differences in the decline of selection gradients with age. Indeed, experimental evolution studies in different species suggest that sex differences in longevity can evolve as a correlated response to selection under changing environments [48-53]. There is also emerging genomic evidence for sex-differential selection on survival and reproduction in humans [54]. However, more work is needed across taxa to establish the generality of the prediction that variation in sex differences in age-specific selection causes the accumulation of sex-specific load in late-acting deleterious mutations.

When the two sexes differ in the timing or duration of reproduction, the age-specific strength of purifying selection will also diverge. In the sex that acquires most of its fitness early, classically males in polygynous systems and/or employing high-mortality mating strategies, the Hamiltonian force of selection will decline more steeply with age, creating a longer late-life "selection shadow" (Figure 1). A longer shadow means that deleterious alleles whose sex-specific effects appear late in life will be less efficiently purged. Over evolutionary time, germline mutations whose deleterious effects affect late-life performance only in the sex that has weaker selection gradients on traits in late-life can accumulate in regulatory regions, producing sub-optimal gene expression that accelerates ageing and shortens lifespan in this sex. This model predicts that the sex with the weaker late-life selection will carry a higher load of late-acting deleterious germline mutations and show broader transcriptional dysregulation during ageing.

Sex-specific mutational penetrance

Alleles whose mutational effects on fitness are concentrated in late-life and have sex-specific mutational penetrance are likely to contribute to the evolution of sex differences in lifespan via mutation accumulation. Hereditary haemochromatosis provides a compelling example of how mutations with late-acting effects can exhibit strong sex-specific penetrance. Haemochromatosis is a hereditary human disease of systemic iron overload caused commonly by mutations in autosomal HFE gene, which encodes for protein involved in iron sensing [55, 56]. Most cases of this disease are associated with missense mutation C282Y, which prevents cells from responding to increased levels of iron by failing to increase production of hepsidin, a hormone that regulates iron levels by reducing iron absorption, resulting in iron overload. Iron overload can lead to a wide range of phenotypic effects, from chronic fatigue to liver disease to hepatocellular carcinomas [55]. The prevalence of C282Y homozygosity varies broadly between different populations from 0.000039% to 1.2%. Mutations in other autosomal genes, including HAMP which encodes for hepsidin, also can cause haemochromatosis but are much rarer [55]. Mutation carriers likely start accumulating increased levels of iron from birth, with clinically significant deleterious effects manifesting only in older, middle-aged adults [57]. This represents an example of a deleterious mutation whose effects on fitness are concentrated in late life, as envisioned by MA theory of ageing.

While the frequency of C282Y homozygosity is similar in both sexes, the penetrance differs strongly with 28.4% of homozygous males developing the disease versus 1.2% of homozygous females [58]. Furthermore, the onset of haemochromatosis starts at around 40 years in men and is most common in postmenopausal women [56, 57]. For example, by 55 years, iron overload resulted in cumulative disease incidence of 14.4% in male C282Y homozygotes versus only 1.2 % in female C282Y homozygotes; this becomes 34.5% versus 9.4%, accordingly, at 65 years. Thus, this recessive autosomal inherited disease has earlier onset and stronger penetrance in males. While there are several potential explanation for this pattern, one of the leading hypotheses is that women shed iron during menstruation which ameliorates impaired iron sensing and prevents overly excessive iron overload [57]. This could provide an example of a deleterious late-acting mutation that affects fitness differently in males and females because it interacts with another sex-specific biological processes. Such autosomal recessive mutations with sex differences in penetrance could be common across taxa, and the direction of sex bias can differ, with some mutations being more detrimental in males, while other in females.

Together, these lines of evidence establish that: the genetic architecture required for sex-specific gene expression is widespread, there is substantial sex-specific genetic variation for lifespan across taxa, and that alleles can exhibit strongly sex-and-age-dependent penetrance. When combined with sex differences in the decline of selection gradients, these features create the conditions required for mutation accumulation to generate sex-differences in ageing without requiring resource allocation trade-offs.

Experimental evolution tests of mutation accumulation theory for sex differences in lifespan and ageing

Whilst strong evidence exists for the existence of the requisite genetic architecture, direct experimental tests are needed to provide evidence for the evolution of sex-specific mutation accumulation. Laboratory evolution studies in which sex-specific selection gradients are manipulated to yield evolutionary responses in sex-specific lifespan and aging could achieve this.

The most direct evidence comes from a study that explicitly manipulated sex-specific selection gradients by increasing early adulthood male mortality in dioecious *C. remanei* for 20 generations, by applying mortality either haphazardly or by selecting males that were best at mate searching [23]. In this species, the reproductive rate of males peaks later in life than in females [59]. In line with evolutionary theory of ageing, males also age later and live longer than females. Experimental manipulation of sex-specific mortality resulted in the rapid evolution of male lifespan – a haphazard increase in early adulthood mortality resulted in the evolution of shorter male lifespan, while female lifespan was unaffected. The effect size was so strong that sexual dimorphism in lifespan that is natural for this species disappeared, and the experimental populations evolved monomorphic lifespan [23]. At the same time, when early adulthood mortality resulted in selection for males that were particularly fast in mate searching, males evolved to be better at finding mates but also evolved longer lifespan, suggesting positive pleiotropy between early-life mating success and late-life survival. Taken together, these results underscore that there is ample sex-specific genetic variation for fitness, lifespan and ageing, and demonstrate how sex differences in the decline of selection gradients on traits with age can lead to rapid evolution of sexual dimorphism or monomorphism in lifespan.

These results illustrate an important additional feature of the sex-specific mutation accumulation model: that specific predictions require a detailed understanding of how interventions affect vital rates. Previous experimental evolution studies manipulating sexual selection, or sex-specific selection, have yielded variable outcomes: effects on lifespan sometimes appear in females only, in both sexes, or in neither [50, 51, 53, 60]. Such variation is expected to evolve according to our model because different experimental treatments alter age-specific reproductive contributions in different ways, thereby generating different selection gradients. Unlike models based only on the perceived strength of sexual selection, the sex-specific mutation accumulation model generates testable and context-dependent predictions once the demographic effects of interventions or ecology are characterized.

Testing mutation accumulation theory

Having established that the genetic requirements exist, and mutation accumulation can cause sexually dimorphic lifespan when selection gradients are sex-specific, we now outline three complementary approaches for testing the model further.

Genomic signatures

Genes predominantly expressed late in life are expected to show weaker purifying selection in the sex with the earlier and/or faster reproductive schedule. Sex-specific mutation accumulation theory predicts excess of deleterious alleles in predominantly late-life acting genes, as well as elevated variation in gene expression in late-life in the sex that is characterized by faster decline in selection gradients. On the other hand, antagonistic pleiotropy theory classically predicts opposite-sign genetic correlations between early-life performance and late-life performance within each sex. Such approaches can be applied to both existing or newly established genomic datasets of natural populations, livestock and humans where there are clear ways to calculate sex-specific selection gradients.

Phylogenetic comparative studies

A potentially fruitful approach for studying the evolution of sex differences in ageing is to use the power of phylogenetic comparative studies. However, future studies will need to resolve the problem that sexual selection can accelerate or postpone male ageing based on the pattern of age-specific reproduction, meaning that the intensity of sexual selection is by itself not a reliable predictor of the direction of evolution of sex differences in ageing. Our suggested approach makes such analyses challenging as it requires the assembly of species-level datasets of sex-specific vital rates and the computation of Hamiltonian forces of selection for each sex. With such data, it is possible to model sex differences in ageing as a function of the difference in decline of selection gradients, rather than by the designated mating system. We predict that the sign and magnitude of the ageing gap between the sexes will correspond directly to the difference in the strength of selection $s(x)$ in old age between the sexes (cf. Figure 1), outperforming classic proxies, such as mating system and sexual dimorphism in body size.

Experimental evolution

Perhaps one of the clearest ways of testing the role of mutation accumulation in the evolution of sex differences in lifespan and ageing will be to modify sex-specific selection gradients experimentally and allow populations to evolve (see also Maklakov and Chen 2014). This approach can be used reciprocally in both sexes, with the theory predicting that sexual dimorphism in lifespan and ageing can be experimentally reduced or increased, depending on the species-specific demography. This approach can be combined with genomic analyses and forward genetics to understand the underlying mechanisms of sex-specific ageing.

Conclusion

Here we reframe our understanding of sexual dimorphisms in ageing and lifespan by recognising mutation accumulation in genes with sex-biased fitness effects as a parsimonious evolutionary mechanism. Rather than requiring sex-specific trade-offs, these dimorphisms can arise as an evolutionary response to differential selection regimes whenever males and females differ in reproductive timing. A key implication of our argument is that understanding sex differences in ageing demands a demographic perspective. Once sex-specific reproductive schedules and survival trajectories are known, the shape of the decline in selection with age follows directly, and with it the expected direction and magnitude of sex differences in mutation accumulation. We therefore predict that, all else being equal, the sex showing earlier onset, or higher rate of early life reproduction, will accumulate a greater burden of late-acting deleterious mutations, exhibit stronger late-life transcriptional dysregulation and, therefore, experience faster actuarial and physiological senescence.

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