Evolution of sex differences in lifespan and aging: Causes and constraints

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Why do the two sexes have different lifespans and rates of aging? Two hypotheses based on asymmetric inheritance of sex chromosomes ("unguarded X") or mitochondrial genomes ("mother's curse") explain sex differences in lifespan as sex-specific maladaptation leading to increased mortality in the shorter-lived sex. While asymmetric inheritance hypotheses equate long life with high fitness, considerable empirical evidence suggests that sexes resolve the fundamental tradeoff between reproduction and survival differently resulting in sex-specific optima for lifespan. However, selection for sex-specific values in life-history traits is constrained by intersexual genetic correlations resulting in intra-locus sexual conflict over optimal lifespan. The available data suggest that the evolution of sexual dimorphism only partially resolves these conflicts. Sexual conflict over optimal trait values, which has been demonstrated in model organisms and in humans, is likely to play a key role in shaping the evolution of lifespan, as well as in maintaining genetic variation for sex-specific diseases.

Keywords:
- aging; disease; mitochondria; senescence; sex chromosomes; sexual conflict; sexual selection

Introduction

Women live longer than men in most countries [1–4] and this phenomenon has attracted considerable cross-disciplinary attention [5–10]. Yet this pattern is a commonplace among mammals and, in general, sexual dimorphism in lifespan is widespread across the tree of life [1, 11–13]. Early biological hypotheses that aimed to explain the sex differences in lifespan centered on the role of sex chromosomes and relied heavily on the fact that recessive deleterious mutations occurring on X (or Z) chromosome are not “guarded” by alleles on the second chromosome in the heterogametic sex. These two non-mutually exclusive processes explain sexual dimorphism in lifespan and aging, essentially, as a maladaptation resulting from asymmetric inheritance [14, 17–19], which leads to increased mortality in a shorter-lived sex.

However, males and females acquire fitness in very different ways [20–24] and another likely possibility is that sexual dimorphism in lifespan and aging is adaptive and results from sex-specific optimization of a tradeoff between reproduction and survival [20, 25–28]. Sexual selection has been increasingly implicated as a major driving force behind sex differences in lifespan in different taxa [11–13, 29, 30], including humans [31, 32], and recent empirical studies provide further support for this hypothesis [33–38]. The realization that sex-specific selection is shaping the evolution of lifespan and aging has brought to light the problem of sexual conflict. Because sexes share most of their genes, the evolution of sexual dimorphism is likely to be constrained [39–42]. Divergent reproductive strategies may drive males and females toward different optima in lifespan, a complex trait affected by many loci. Consequently, alleles residing in the same loci can be selected in opposing directions in males and females, resulting in sexually antagonistic selection (SAC) [26, 40]. Apart from potentially preventing the sexes from reaching their respective life-history optima, such selection would maintain genetic variation.
variation for lifespan in the population [1, 43, 44], which can have important evolutionary and medical implications.

Our goals here are two-fold. First, we briefly review the state-of-the-art in the study of sex differences in lifespan and aging with an emphasis on several recent contributions that directly tested the key hypotheses in this regard and suggest that sex-specific selection has the most empirical support to date. Second, we build on the newly available data on model organisms and humans to propose that sexual conflict plays a key role in the evolution of lifespan and aging and discuss potential implications for life-history evolution and medical interventions aimed at lifespan extension.

Asymmetric inheritance: Unguarded X and mother’s curse

Males are the heterogametic sex and live shorter than females in humans, mice, and Drosophila fruit flies. Such sex-specific mortality is often proposed to result from the heterogametic sex being biologically burdened by expression of recessive deleterious mutations, such as hemophilia in humans, located on unpaired (“unguarded”) X (Z) sex chromosomes [6]. This idea fits with the observation that in birds, where females are the heterogametic (ZW) sex, mortality is generally female-biased. However, a closer look at the phylogenetic distribution of sex-bias in mortality does not necessarily support this hypothesis. Apart from heterogamy, mammals and birds differ also in their mating systems: while mammals are generally polygynous with high costs of male-male competition, most birds are monogamous with less intense male-male competition, and polygynous species of birds often show male-biased mortalities [13] despite female heterogamy.

There have been few explicit experimental attempts to evaluate the generality of “unguarded X” for sex differences in lifespan. One prediction of this hypothesis is that inbreeding, which increases homozygosity, should affect males less than females. Two independent quantitative genetic studies using the seed beetle Callosobruchus maculatus indeed found that male lifespan is affected by inbreeding less than female lifespan [45, 46]. However, there was a crucial twist: in the second study, where beetles experienced higher levels of inbreeding and were kept in same-sex cohorts, inbred males lived longer than outbred males across two different experiments despite showing 47% reduction in fitness [46]. Because inbred females lived shorter than outbred females, inbreeding thus reduced, and in one of the trials essentially eliminated, sex difference in lifespan. These results contradict the predictions from “unguarded X” hypothesis and suggest that lifespan and fitness are negatively correlated in males. Consequently, based on both comparative and experimental evidence, “unguarded X” is unlikely to provide a general explanation for sex differences in lifespan [6].

Maternal inheritance of mitochondrial genetic material is another form of asymmetric inheritance that could potentially result in increased male mortality [4, 14]. Theoretically, mutations that are substantially harmful to males can accumulate in mitochondrial genomes if they are only slightly deleterious, neutral or beneficial to females [4, 15, 16, 47]. For example, Leber’s optic neuropathy is a maternally inherited mitochondrial disease that predominantly affects males [15]. A recent study showed that variance in naturally occurring mitochondrial haplotypes in Drosophila melanogaster fruit flies affected lifespan and mortality rates in males but not in females, which is consistent with the idea of mutation load in mitochondrial genome affecting male aging [4]. However, earlier studies showed variation in mtDNA affecting lifespan and aging in female Drosophila [48, 49]. More studies are needed to test whether mitochondrial mutation load results in increased variation in male aging compared to female aging in different taxa. Furthermore, even though mitochondrial genes are not likely to be selected in males (but see [50, 51]), the nuclear genes that may affect the expression of mitochondrial genes definitely are. Therefore, it is possible that males will evolve ways to counteract the negative consequences of the mitochondrial mutation load, as has been recently suggested for mitochondrial effects on male fertility [52]. For example, “mother’s curse” might be resolved via sex-specific expression of nuclear duplicates of mitochondrial genes. Suggestively, nuclear duplicates of OXPHOS genes have testis-biased expression in D. melanogaster and D. yakuba [53, 54]. Thus, while the possibility of certain male-specific diseases to result from mitochondrial mutation load is quite likely [15], and there is strong experimental evidence that variation in mtDNA affects male aging [4], it remains unclear to what extent maternal inheritance of mtDNA can be considered a leading biological mechanism behind the sex difference in lifespan and aging. Mitochondrial genomes are maternally transmitted also in taxa where mortality is generally female-biased, such as birds. Even in D. melanogaster fruit flies and Callosobruchus maculatus seed beetles, both model organisms used to study sex differences in lifespan, females live longer than males only under some conditions but not always [55, 56]. Males generally outlive females in C. elegans and other Caenorhabditis worms that are both hermaphroditic and dioecious [57]. In Drosophila simulans, females have lower survival than males and show higher rates of mitochondrial reactive oxygen species (ROS) production and lower catalase production, suggesting increased mitochondria-induced damage and lower rate of damage repair [58]. Finally, while the mismatch between mitochondrial DNA and nuclear DNA has been shown to affect lifespan, it does not necessarily decrease it [59]. Rand et al. [59] showed that even mitochondrial haplotypes from a different species (D. similans mtDNA introgressed in D. melanogaster) may extend longevity in different nuclear backgrounds. These results suggest that sex differences in lifespan are not necessarily a result of maladaptation affecting shorter-lived sex, such as an accumulation of male-damaging mutations in mitochondrial genome, but perhaps a result of sex-specific selection optimizing life-histories differently for males and females.

One problem that is common to all asymmetric inheritance theories of sex differences in lifespan is that they implicitly equate long life with high fitness. However, given a well-established tradeoff between reproduction and survival and the fact that natural selection maximizes fitness rather than survival per se, it is easy to see how selection can result in females having higher ROS production and being
shorter-lived than males in some taxa [58] even when females are the homogametic sex and mtDNA is maternally inherited. The study discussed above by Camus et al. on D. melanogaster fits with this view. Increased mitochondrial mutational load in males could contribute to variation in sexual dimorphism in lifespan in different taxa by either increasing or decreasing the gender gap. First, mutations deleterious to male fitness could actually increase male lifespan. For example, in populations where selection favors high metabolic rate and short lifespan in males, selection favoring low metabolic rate in females could increase male lifespan at the expense of male fitness. Second, even in cases where mitochondrial male-specific disease is actually detrimental to male lifespan, mutation load can either increase or decrease the gender gap depending on whether males generally live longer or shorter in any given species or population. Thus, the role of mtDNA in the evolution of sexual dimorphism is likely to be complex and the existing data do not support the prediction that males live shorter or age faster than females across taxa.

### Adaptive sex-specific selection in both sexes generates sexual dimorphism

The most fundamental difference between the sexes lies in the size of their gametes – numerous but small male sperm compete for the access to a few but large female eggs. In fact, sex can be defined by the size of the gamete produced by the organism [60, 61]. Anisogamy (gametic dimorphism) underlies the evolution of differential reproductive strategies between the sexes, resulting in the evolution of sexual dimorphism in many morphological, behavioral, physiological, and life-history traits [20, 23, 24, 60, 62]. Because of the differences in reproductive strategies, sexes can suffer from different extrinsic mortality across taxa [6, 25, 26]. Sexual selection can result in increased male mortality due to conspicuous male displays (costly in terms of energy expenditure and increased predation) or direct injury in combat or competition in polygonous species [11, 13, 29, 32, 35, 37, 63]. Conversely, in species with reversed sex-roles, sexual selection can give rise to higher extrinsic mortality in females [64, 65]. Females can also experience higher extrinsic mortality rate due to exposure to high rates of predation because of parental care (e.g. incubating birds) [13]. Finally, the interactions between the sexes can directly affect lifespan and aging, and adaptive evolution in one sex can affect senescence in the other sex [66].

Sexual selection can thus have profound effects on lifespan under natural conditions. But what about intrinsic longevity and aging? An early insight by George Williams was that the sex suffering from higher rate of extrinsic mortality in the wild should undergo more rapid senescence [25]. This supposition is a special case of a central prediction of the evolutionary theory of aging, which maintains that increased extrinsic mortality will lead to the evolution of more rapid senescence in a population [25, 67–69]. For example, in polygynous red deer (Cervus elaphus), males compete for access to females and exhibit faster reproductive aging [37]. In general, at least in polygynous vertebrates, increased extrinsic male mortality is associated with demographic indices of more rapid senescence [35].

However, recent theoretical advances in the evolutionary theory of aging cast doubt on whether increased extrinsic mortality per se should always lead to the evolution of rapid aging as envisioned by early theoreticians. When extrinsic mortality is non-random and depends on individual condition, then increased mortality will result in increased selection [70–74]. If senescence in a trait increases an organism’s susceptibility to a certain environmental hazard, then increased environmental hazard may actually select against senescence in this trait [71, 72]. While the importance of such condition-environment interactions for the evolution of aging has been shown experimentally [75], it remains to be tested with respect to sex differences in longevity and aging. Meanwhile, there are some indications that evolution of increased male longevity is possible even under male-biased extrinsic mortality rate. For example, in black field crickets (Teleogryllus commodus), males advertise their presence to females by producing conspicuous calling which may last for hours. Male crickets suffer higher mortality and have shorter lifespan than females under semi-natural conditions [76]. However, males live longer and age slower than females in the laboratory when protected from abiotic and biotic hazards of their natural environment [76]. This result is in line with the idea that increased selection on males resulted in more physiologically robust phenotypes allowing males to outlive females in the benign environment. Furthermore, several arguments have been put forward that in humans, where females typically outlive males, males may suffer from increased extrinsic mortality but not necessarily from more rapid aging [9, 31]. This idea makes sense because human males, but not females, retain reproductive potential until very old age [31].

One way in which sex-specific selection, and in particular sexual selection, can affect male mortality and contribute to sexual dimorphism in lifespan has to do with sex-specific hormones. There is little data on the role of hormones on sex-specific mortality in nature, but some insight may be gathered from the data on castration of domestic animals and, unfortunately, of humans. Some of the results are striking. Gonadectomy reportedly equalized lifespan of male and female cats (5.3 and 7.7 years in intact cats versus 8.1 and 8.2 years in castrated cats, respectively) [6]. In humans, there are some (rather gruesome) data to suggest that removal of sex hormones similarly increases male lifespan. Castration increased lifespan among mentally ill institutionalized males [77]. Interestingly, the increase in lifespan was apparently caused by lower baseline mortality rate in castrated males [78]. A recent study further explored this issue by analyzing data on lifespan of eunuchs in Korean Imperial court [79]. Eunuchs lived 14.4-19.1 years longer that non-eunuchs of similar status [79]. This range is similar to a previously reported increase of 13 years in castrated men in 20th century Kansas [6]. The role of sex-specific hormones in determining sex-specific lifespan is one of the strongest arguments against the leading role of asymmetric inheritance in the evolution of sex differences in longevity and aging [6, 20].

The key role of adaptive sex-specific selection in generating sexual dimorphism in lifespan suggests that medical interventions aimed at prolonging lifespan in model organisms and humans are likely to have sex-specific effects. Indeed, dietary restriction (DR), the most successful treatment to date to robustly increase lifespan in a wide range of taxa [80, 81], affects sexes differently in at least two different model systems [82, 83]. Moreover, recent data show that the effect of DR on sex-specific lifespan in *D. melanogaster* also interacts with social context, suggesting that lifespan-extending treatments should take into account not only the sex but also the reproductive status of the organisms [84]. Most suggestively, a study that treated mice with rapamycin, a drug that extends lifespan in different taxa by reducing nutrient-sensing signaling, which is approved for clinical use as immunosuppressant in humans, showed substantially different effects on males and females [85–88]. Given that rapamycin is currently considered the most promising anti-aging drug and its potential for clinical use in this capacity in humans is under extensive research [69], the sex-specificity of its lifespan extension effect requires further investigation.

Sex-specific selection provides a general explanation for the evolution and expression of sex differences in lifespan and aging. However, making a prediction regarding the pattern of sex-specific aging in a given population requires a deep knowledge of ecology and evolutionary history of the organism. In particular, any meaningful prediction regarding sex differences in longevity and aging rates should be based on (i) the rates of extrinsic mortality in each sex; (ii) the primary agents of mortality (e.g. predators, diseases, abiotic factors); and (iii) whether mortality is primarily random or condition-dependent. We suggest that experimental evolution approach can be used to improve our understanding of the evolution of sexual dimorphism in aging. For example, extrinsic mortality rates can be manipulated in one sex in random or condition-dependent manner to test how mortality rate (high versus low) and mortality type (random versus condition-dependent) affect the evolution of sex-specific longevity and reproductive senescence. We predict that increased mortality rate would result in the evolution of reduced longevity and accelerated senescence in a focal sex under random mortality but increased longevity and postponed senescence under condition-dependent mortality that selects for physiologically robust organisms [75, 90]. Under both scenarios, a change in sex-specific extrinsic mortality rate is predicted to affect sexual dimorphism in aging.

**Sexual conflict constrains adaptive sexual dimorphism in life-history traits**

In the preceding paragraphs, we have argued that optimal values for lifespan are likely to differ between the sexes because of the differences in reproductive strategies. Which sex lives longer will depend on the idiosyncrasies of the mating system, but this is less important for the key argument that we want to develop here. Differences in optimal life-histories can result in inter-locus sexual conflict (IRSC) over reproductive schedules and selection in one sex can affect longevity in the other sex. The classic examples of male traits that affect female longevity include ejaculate size, accessory gland proteins (ACPs), and genital armor [91]. However, there is a different type of sexual conflict that is likely to play an important role in the evolution of aging. Because the vast majority of genes are shared between the sexes, the evolution of sexual dimorphism is inherently constrained when alleles at the same loci are selected in opposite directions when residing in different sexes. Such intra-locus sexual conflict (IASC) can be resolved by the evolution of “modifier” genes that control sex-specific gene expression. However, the evolution of such “modifiers” is predicted to be slow [39, 92, 93] and theory maintains that IASC will play a substantial role in male-female co-evolution [40, 41, 94]. In line with this, empirical evidence also suggests that the evolution of sexual dimorphism provides only partial resolution of IASC [43, 44, 94–97]. Thus, IASC is predicted to constrain the evolution of morphological, behavioral, and life-history traits and to maintain genetic variation in the populations [40, 41, 94]. In recent years, strong empirical evidence for the prevalence of IASC across different taxa has started to accumulate [41, 94]. The classic work by Chippindale et al. [98] demonstrated negative genetic correlation for reproductive success of males and females across 40 haploid genomes in *D. melanogaster* fruit flies. Subsequently, negative intersexual genetic correlations for fitness have been reported in both laboratory studies and in natural populations, suggesting that IASC indeed plays a fundamental role in the evolution of sexual dimorphism in life-histories [94, 97, 99–104]. Therefore, the key implication of sex-specific selection on lifespan and rates of aging is that differences in optimal trait values are likely to result in sexual conflict over these traits.

Despite such strong theory-driven prediction and empirical demonstration of the general importance of IASC for sex-specific fitness, the role of intra-locus conflict in the evolution of lifespan and aging remained largely unexplored until recently, perhaps because an early study failed to identify a signature of IASC on aging using quantitative genetic approach in black field crickets [105]. However, two recent studies identified intra-locus conflict over lifespan in two different taxa using rather different experimental approaches. In particular, Lewis et al. [44] used a quantitative genetic approach to show that selection on three sexually dimorphic life-history traits, including longevity, is working in the opposing directions in female and male Indian moths *Plodia interpunctella*, and that the sex-specific response to selection is constrained by the genetic variance-covariance matrix. In *P. interpunctella*, male fitness is maximized by fast development time and increased adult longevity, while the opposite is true for females [44]. This study thus suggests that if males in this system were exposed to strong sex-specific selection on increased longevity, then female longevity would co-evolve via the intersexual genetic correlation and, as a result, male fitness would increase while female fitness would decrease. Such an experiment has been conducted in a different study system, the seed beetle *Callosobruchus maculatus*, where divergent sex-specific selection on male lifespan has been applied to create replicate lines with
long-lived and short-lived males [43]. Because of the intersexual genetic correlation for lifespan, selection on males caused female lifespan to co-evolve along the same trajectory. However, in *C. maculatus*, long lifespan is associated with low male fitness and high female fitness [46]. Therefore, selection for long-life resulted in low male fitness/high female fitness populations [43]. These studies directly show that the evolution of sex-specific lifespan in at least two different study organisms is severely constrained by intersexual genetic correlation resulting in sexual conflict (Fig. 1). It is particularly interesting that in both cases IASC occurs despite sexual dimorphism in lifespan, suggesting that sex-specific selection played an important role in the evolutionary past of these two species but failed to fully resolve the conflict over this trait. Given how fast the response to strong sex-specific selection on lifespan was obtained (just five generations), we suggest that similar studies can be done on a range of suitable model organisms (such as fruit flies, neriid flies, other species of seed beetles, nematodes). Population genetic studies can be fruitfully applied to study IASC in nature using long-term datasets of individually marked animals (also see below). Such studies are needed in order to establish the generality of IASC over lifespan and aging across taxa.

**Sexual conflict and human health**

Women commonly outlive men, at least in recent history [2]. Sex difference in human lifespan and its social, demographic, and societal consequences have been intensively studied from multidisciplinary perspective [2, 78, 106, 107]. However, the evolutionary forces behind the sexual dimorphism in human lifespan have received relatively little attention (but see [9, 31, 32]). The knowledge of such evolutionary forces does not lie exclusively in the realm of fundamental science, but is also necessary to understand how genetic constraints resulting from either past adaptations, or from the action of contemporary selection, may affect lifespan interventions in modern humans. Moreover, such knowledge could improve our ability to assess environmental and cultural effects on sex differences in lifespan and to understand the between-country differences, which can be substantial [10].

Evidence for sex differences in the manifestation of aging in different traits in humans has so far been conflicting. For example, while males suffer from higher mortality rate, females appear to become presbyopic (lose elasticity in the lens of the eye preventing focus to short distance) earlier and faster than men and their reaction time to auditory stimuli declines faster too (reviewed in [9]). Overall, the notion that men age faster than women appears to be far from straightforward: women have higher age-specific survivorship than men, but among the survivors, health status tends to be better in older men than women [9].

Recent studies measuring selection on lifespan in both sexes in historical human populations support the idea that sexual dimorphism could result from SAC in the past. Such studies suggest that prolonged life has different fitness consequences for women and men. Women worldwide experience irreversible cessation of reproductive function with menopause around the age of 50 years, that is suggested to evolve due to increasing reproductive conflict over age with own offspring [108, 109] and because of genomic conflict between autosomal genes and genes situated in the X chromosome (caused by their differential inheritance patterns) over the optimal age at menopause [110]. Women thus stop accruing fitness through production of direct offspring, but increasing evidence suggest that a longer post-reproductive lifespan in women is associated with increased fitness via her own offspring and therefore with the production of more grandchildren being born [3]. This is because the presence of a post-menopausal “helper” in the household is often linked with more successful reproduction in a woman’s own offspring and therefore with the production of more grand-offspring (reviewed in [111]). In contrast, the...
evidence for benefits of grandfather presence for grandchild survival is far less consistent amongst the different populations investigated so far [111]. For example, in Finland, analyses of historical data showed that grandmother presence improved grandchild birth rate and survival resulting in women gaining on average two extra grandchildren for each decade they survived beyond menopause age until around age of 75 [3], but grandfather presence was not associated with grandchild survival and men in this population gained no fitness benefit from post-reproductive longevity [112, 113]. Consequently, the “optimum” longevity peaked earlier for men than for women.

In Finland, such effects arose because of the lack of grandfather benefits [112] combined with a monogamous mating system where men could only increase their fitness through direct reproduction at old ages by remarriage after a death of their spouse (no divorce permitted). Such remarriage and continued reproduction at older ages, when the first wife’s menopause would have normally limited reproduction opportunities, indeed increased the lifetime number of offspring sired by these men by lengthening their reproductive period [113]. However, reproduction with a subsequent wife had such a negative influence on the survival and mating opportunities of the offspring born in the first marriage, that overall there was a negative effect of male lifespan beyond the age of 50 on the overall number of grand-offspring produced [113]. These findings are suggestive of a potentially SAC on human lifespan, at least in some societies. Nevertheless, although both lifespan and fitness are known to exhibit significant heritable components in many human populations leaving room for evolutionary response to selection [114], the genetic basis of the sexual conflict over lifespan in humans has not yet been elucidated. Ongoing research however suggests that selection on lifespan in the historical Finnish population was operating in opposing directions in males and females (Bouwhuis and Lummaa, unpublished data): this observation parallels the data from the model organisms that we discussed above.

In polygamous populations, men can potentially gain fitness via direct reproduction in older age through simultaneous marriage to several different-aged wives [115]. Therefore, SAC may act less strongly on lifespan in such populations, and sexual dimorphism in lifespan may be smaller as a consequence. However, such reproductive patterns may also impose quality-quantity tradeoffs on offspring that might compromise the long-term fitness benefits of increased reproductive rate [116] and typically only a small proportion of men succeed in marrying polygynously. On the other hand, reduced female fecundity is correlated with reduced sexual dimorphism in human lifespan across different countries [10]. It would thus be of interest to quantify sex-specific selection pressures on lifespan and elucidate its underlying genetics in human populations with differing mating systems to address this question.

Recently, Stearns et al. [117] used the ongoing Framingham Heart Study [118] to show that evolution of contemporary men and women is genetically constrained by IASC over several important traits, including height, weight, age at first birth, and total cholesterol levels. While this study did not explicitly look at sexual conflict over lifespan, it has some important implications for the potential of sexually antagonistic co-evolution to maintain genetic variation in sex-specific disease. First, the authors showed that contemporary selection favors shorter women and taller men, because such individuals gain higher lifetime reproductive success. Second, they identified a negative genetic correlation between female height and total cholesterol in men. Third, they showed that selection acting to reduce total cholesterol in women. These three findings suggest that selection acting to reduce female height could potentially maintain higher total cholesterol in males, despite selection for reduced total cholesterol in females because genes related to short height when expressed in females also promote higher cholesterol levels when expressed in males. High cholesterol is likely to be detrimental for longevity as it can cause disease. While females presumably trade short height (associated with high fecundity) for high total cholesterol, correlated selection for increased total cholesterol would be detrimental for male health, although not necessarily for male fitness.

Conclusions

Sex differences in lifespan and aging are ubiquitous. Assymmetric inheritance theories (“unguarded X” and “mother’s curse”) are comprehensive explanations for sexual dimorphism in lifespan that make clear testable predictions. However, these predictions are not well-supported in empirical studies. We argue that sex differences in lifespan and aging rates are adaptive and shaped by sex-specific selection driven by sexually dimorphic life-histories. Sex-specific selection for different optima in life-history traits, coupled with positive intersexual genetic correlation for these traits, leads to IASC. This conflict is predicted to have two effects: (1) to prevent the sexes from reaching their optimal lifespan; (2) to maintain genetic variation for lifespan and sex-specific disease in the populations. Therefore, pharmacological interventions aimed at prolonging human lifespan are predicted to have different, at times opposing, effects on reproductive performance in men and women.

Acknowledgements

We thank Göran Arnqvist, Damian Dowling, Urban Friberg and Stephen Stearns for suggestions that improved the paper. AAM was supported by ERC Starting Grant 2010 and the Swedish Research Council and VL by ERC Starting Grant 2008 and Royal Society University Research Fellowship.

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