

# Sex Differences in Longevity and in Responses to Anti-Aging Interventions: A Mini-Review

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## Key Words

Sexual dimorphism · Insulin-like growth factor · Life expectancy · Sex differences · Anti-aging · Female longevity bias · Mechanistic target of rapamycin

## Abstract

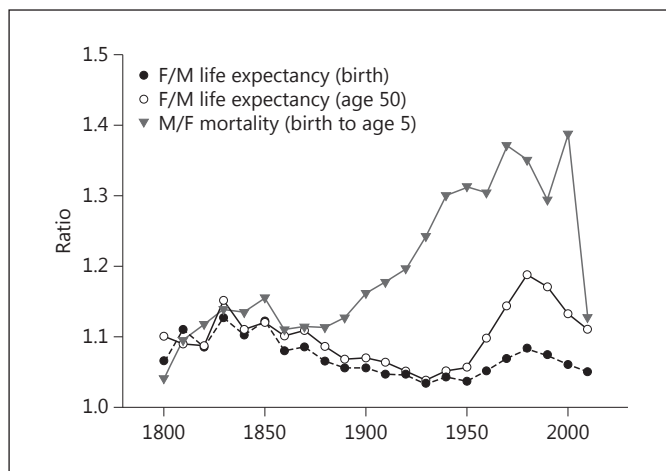
A robust, often underappreciated, feature of human biology is that women live longer than men not just in technologically advanced, low-mortality countries such as those in Europe or North America, but across low- and high-mortality countries of the modern world as well as through history. Women's survival advantage is not due to protection from one or a few diseases. Women die at lower rates than men from virtually all the top causes of death with the notable exception of Alzheimer's disease, to which women are particularly prone. Yet, despite this robust survival advantage, women across countries of the world suffer worse health throughout life. The biological mechanisms underlying either longer female survival or poorer female health remain elusive and understudied. Mechanisms of mammalian biology, particularly with respect to aging and disease, are most easily studied in laboratory mice. Although there are no consistent differences in longevity between mouse sexes even within single genotypes, there are often substantial differ-

ences in individual studies, sometimes favoring females, other times males. Investigating the environmental causes of this puzzling variation in longevity differences could prove illuminating. Sex differences in response to life-extending genetic or pharmacological interventions appear surprisingly often in mice. Longevity enhancement due to reduced signaling through IGF-1 or mTOR signaling typically favors females, whereas enhancement via a range of pharmacological treatments favors males. These patterns could be due to interactions of the interventions with sex steroids, with adiponectin or leptin levels, or with the sex differences in immune function or the regional distribution of body fat. Clearly, generalizations from one sex cannot be extended to the other, and inclusion of both sexes in biomedical studies of human or other animals is worth the effort and expense.

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## Introduction

Recent biomedical and demographic research has provided numerous examples of major sex differences in physiological characteristics unrelated to reproduction and in responses to genetic, nutritional, or pharmacological interventions. The renewed appreciation of the mag-



**Fig. 1.** Female survival advantage (Sweden from 1800 to 2010). Note that the sex ratio of all three metrics is always greater than 1, indicating better female survival. F = Female; M = male. Source: Human Mortality Database ([www.mortality.org](http://www.mortality.org); accessed October 30, 2014).

nitude and importance of the impact of sexual dimorphism on the results of both ‘basic’ and clinical studies leads to novel and, in some cases, unexpected insights.

It is in this context that this article briefly reviews the evidence that life expectancy and patterns of age-related disease exhibit great and amazingly consistent differences between women and men, that the impact of sex on longevity of common laboratory mammals is very different, and that responses to life-extending (‘anti-aging’) interventions can be very different in females than in males.

Women live longer than men at all times and everywhere. An examination of The Human Mortality Database ([www.mortality.org](http://www.mortality.org)), which provides detailed historical population demographic records from 37 countries with particularly reliable data, reveals that women experienced greater life expectancy at birth than men in every one of those countries for every year on record. An extensive and enlightening example is Sweden, which has more complete and reliable demographic records than any other country. Since 1800, when life expectancy at birth was 33 years for women and 31 years for men, to today when it is 83.5 years for women and 79.5 years for men, women lived longer than men in every single year (fig. 1). In fact, as figure 1 also shows, from the age of 50 years, women also lived longer than men in every year. So this consistent life expectancy difference is not due to early deaths such as those due to war or infant diseases. In fact, even as infants, females survive better than males.

Male mortality in Sweden from birth to the age of 5 years was greater than female mortality in 1800, when one third of babies died by their 5th birthday, and it is still true today, when far less than 1% of babies die between birth and the age of 5 years. This remarkably consistent survival advantage of women compared with men in early life, in late life, and in total life is not confined to Sweden but is seen in every country in every year for which reliable birth and death records exist. There may be no more robust pattern in human biology.

A variety of cultural, environmental, and socioeconomic factors will affect the magnitude of sex differences in life expectancy though. Among modern, industrialized countries, the gender gap in life expectancy ranges from about 4 years (e.g. Israel and the Netherlands) to more than 10 years in the countries of the former Soviet Union. Men not only consistently have higher mortality rates than women, they also have consistently greater variation in mortality than women among subpopulations [1]. That is, some subpopulations of men are considerably worse off than similar subpopulations of women, which would have the effect of increasing the size of the gender gap in life expectancy. To the extent that subpopulation differences are reduced, the gap will narrow. A good example of this is shown in an analysis of life expectancy among the 3,143 counties in the USA, which finds an 18-year difference in life expectancy between men in the longest-lived and those in the shortest-lived counties compared with only a 13-year difference for women [2]. Similarly, the education (or its lack) has a greater impact on male than on female life expectancy [3].

As should not be surprising given the robustness of this pattern, women die at lower age-adjusted rates than men from a broad range of diseases. For instance, in the USA, in 2010 women died at lower rates than men of 12 of the top 15 causes of death [4]. Two causes (stroke and Parkinson’s disease) were approximately equal between the sexes. Women died at higher rates than men only of Alzheimer’s disease.

Several hypotheses have been put forward to explain the gender gap in life expectancy. For instance, by several measures women have a more responsive immune system than men [5, 6]. As inflammation is now implicated in many diseases, differences in inflammatory responsiveness could conceivably play a role in the gender gap. Another possibility is that sex hormones may be involved, either men’s reproductive hormones increasing susceptibility to a host of diseases or women’s hormones providing resistance to diseases. Some evidence – not the strongest evidence, however – supports the hypothesis of the

life-shortening impact of men's hormones. Specifically, longevity records from 81 Korean eunuchs who lived at the royal court in the 16th to 19th centuries found that eunuchs lived 15–20 years longer than contemporary intact controls [7]. The size of this difference is nearly the same as 20th-century records recovered from an American institution for the mentally retarded, in which castration of both men and women was performed, mainly for behavioral reasons [8]. Comparison of 297 castrated men with 735 intact men from the same institution revealed that on average the castrated men lived 13.6 years longer than the intact men. Moreover, the earlier in life men were castrated, the longer they lived. For women, the prediction from the sex hormone hypothesis would be that removal of ovaries should reduce longevity. However, a comparison of 23 oophorectomized with 309 intact women did not uncover any significant difference in longevity. Another prediction from the same hypothesis suggests that postmenopausal women receiving hormone replacement should outlive women eschewing hormone replacement. No evidence for such an effect exists. In fact, existing evidence suggests that the opposite might be true [9].

Examination of sex differences in *health* paints a somewhat different picture than sex differences in *survival* though. Across countries, including both low- and high-income countries, women display higher overall rates of physical illness than men at all adult ages. They experience more disabilities and activity limitations. For instance, women in high-income countries are more likely than men to report difficulties in walking, climbing stairs, dressing, and other common activities. In low-income countries, women report greater difficulties than men in a wide range of common activities such as bending over, pumping water, or walking a specified distance. In addition, women make more doctor visits, spend more days hospitalized, and take more medications than do men [10–12]. Even in Russia, which has one of the largest sex differences in life expectancy in the world, with a male disadvantage of more than 10 years, males report better health and physical functioning at ages of 55 years and higher [13].

Several hypotheses have been proposed to attempt to explain this health-survival paradox. One hypothesis could be called the differential selection hypothesis. It posits that men are more likely than women to die of similarly serious diseases; therefore, surviving men will be healthier than surviving women. Unfortunately, there is scant evidence to support this hypothesis. A more plausible hypothesis is that women are more sensitive to physical discomfort and are more likely to seek medical atten-

tion when it occurs. However, empirical support for explanations of this type is scant and uneven [11]. Moreover, this paradox is not seen only in wealthy, industrialized countries, where cultural norms might make such explanations most plausible. It is also found in places such as Jamaica, Malaysia, and Bangladesh, where access to medical care and treatment is particularly difficult for either gender [14, 15]. At least part of the health-survival paradox can be uncontroversially attributed to the higher prevalence and severity of arthritis and musculoskeletal disease among older women. To what this higher prevalence and severity itself can be attributed is not obvious, however.

How general is the female longevity bias among other animal species? Is it an idiosyncrasy of human biology or a general pattern within mammals? This question proves surprisingly difficult to answer. A key consideration is whether one focuses on wild or captive populations. Patterns of sexual differences in aging and longevity evolved, of course, under conditions in nature. On the other hand, mortality patterns in wild populations are dominated by extrinsic causes such as climatic events, competitive interactions within and between species, parasites, infectious diseases, and predation, all of which can mask intrinsic physiological differences. Given this caveat, in nature, females of socially polygynous species such as African lions or red deer – which include a large majority of mammals – often live longer than males. By contrast, survival is approximately equivalent or males live somewhat longer in socially monogamous species, such as most birds and a few mammals such as African wild dogs [16].

Among higher primates (monkeys and apes), females are generally longer-lived than males in wild populations [17]. In captive populations, however, the picture is more complex. In some monkey species, particularly those in which males contribute significantly to parental care, captive males live longer than captive females [18]. In other species – such as baboons, which have extensive captive demographic records – there appears to be no sex difference in longevity [19]. These various patterns among species suggest that the heterogametic sex hypothesis is unlikely to be valid. There is no single difference in life expectancy that applies to all mammals.

Importantly though, in apes (chimpanzees, gorillas, orangutans, and gibbons), our closest evolutionary relatives, females appear to uniformly live longer than males both in the wild and in captivity [18, 20]. Thus, humans appear to have inherited from our ape-like ancestors our propensity for women to outlive men. The mechanism(s) underlying this sex difference remain speculative though.

**Table 1.** Some studies showing major sex differences in response to life-extending interventions

Genotype/treatment	Male increase	Female increase	Reference
IGF-1R heterozygote	0	++	Holzenberger et al. [30], 2003
IGF-1R heterozygote	0	+	Bokov et al. [31], 2011
IR heterozygote	+	0	Nelson et al. [48], 2012
IRS1 knockout	0	++	Selman et al. [32], 2008
RIIb (PKA) KO	++	0	Enns et al. [49], 2009
Overexpress Sirt6	++	0	Kanfi et al. [50], 2012
S6K1 knockout	0	++	Selman et al. [34], 2009
mtor <sup>+/-</sup> ; mlst8 <sup>+/-</sup>	0	+	Lamming et al. [44], 2012
NDGA	+	0	Strong et al. [38], 2008
Aspirin	+	0	Strong et al. [38], 2008
Acarbose	++	+	Harrison et al. [39], 2014
17- $\alpha$ -Estradiol	+	0	Harrison et al. [39], 2014

0 = No change; + = small, significant change; ++ = large, significant change.

### Sex Differences in Longevity in Mice

Among mammals, mechanistic studies are most easily done in laboratory mice. Could mice be informative as to sex differences in longevity? The literature on aging is beset with confusion as to the existence or nature of sex differences in survival in mice [21]. One can find claims that males are the longer-lived sex [22], that there is no sex difference [23], and that females live longer [24]. It turns out that all of these authors are correct. That is, sex differences in mouse longevity vary greatly. Austad [21] summarized 118 mouse survival studies that reported either mean or maximum longevity in both sexes. Results of any dietary or genetic treatments were ignored and only the ‘control’ longevity considered. In 65 (55%) of the studies, male longevity exceeded that of females, but 51 (43%) of the studies found the reverse. The majority of these longevity differences tended to be small. However, about 10% of the studies reported differences of 20% or more, and these studies were about equally divided between greater male versus greater female longevity.

One obvious explanation for this variation is the mouse genotype. All inbred laboratory mouse strains have their idiosyncrasies. However, 29 different studies of the single C57BL/6 strain found almost as great a variation in longevity differences between the sexes as for the entire 118-study data set [21]. Longevity differences in both directions also were reported in DBA/2 and BALB/c mice, among F1 genotypes, in mixed genotypes, and even among wild-derived mouse stocks. Clearly, subtle differ-

ences between laboratory environments or husbandry practices can have a substantial impact on sex-specific survival. If we could identify the source or sources of this variation, it could potentially teach us a lot about sex differences in aging.

### Sex Differences in Life-Extending Interventions in Mice

Life-extending interventions are multiplying rapidly in mice, and a surprising number of these impact only one sex or impact one sex considerably more than the other (table 1). Calorie restriction, transgenic overexpression of the ‘hunger hormone’ fibroblast growth factor 21 (FGF-21), targeted deletion (‘knockout’) of growth hormone-releasing hormone (GHRH) or growth hormone (GH) receptors, and hereditary deficiency of GH, prolactin, and thyrotropin extend longevity in both female and male mice [25–29]. A thorough review of all published mouse and rat calorie restriction studies which distinguished the results by sex found median longevity to be extended by 12% on average in male mice, by 16% in female mice, by 31% in male rats, and by 26% in female rats [25]. However, reduction in the levels of the key mediator of GH actions, insulin-like growth factor 1 (IGF-1) [30, 31], or deletion of various genes acting ‘downstream’ from GH and IGF-1 receptors extends longevity in females only or has a markedly greater effect on lifespan in females than in males. This includes mice with deletion of insulin receptor substrate (IRS1) [32], brain-specific deletion of IRS2 [33], or deletion of S6 kinase 1 [34], an important target of the mechanistic target of rapamycin (mTOR).

A particularly interesting example of sex-specific effects of genetically manipulating endocrine signaling on longevity is provided by mice heterozygous for the deletion of the IGF-1 receptor. In 2003, the Holzenberger laboratory reported a major (approx. 33%) extension of lifespan in *Igf1r*<sup>+/-</sup> females, with a similar but smaller and statistically nonsignificant trend in males [30]. Eight years later, a paper from the Richardson laboratory reported that heterozygous deletion of the same gene in a different strain of mice (C57BL/6 rather than 129/SvPas) resulted in a significant but much smaller (approx. 5%) extension of longevity in females and a trend for reduced longevity in males [31]. Earlier this year, Xu et al. [35] from the Holzenberger group confirmed that C57BL/6 IGF-1R<sup>+/-</sup> females live longer than controls, while males exhibit a reduction in maximal lifespan. Importantly, these investigators related differences between lifespan extension they



produced in C57BL/6 and 129/SvPas mice (11 vs. 33%) to quantitative differences between these two strains in IGF-1 signaling and in the response of this signaling pathway to heterozygosity for IGF1R deletion.

We are not aware of any studies aimed specifically at explaining sex differences in the impact of genetic suppression of the IGF-1, insulin, or mTOR pathways on aging and longevity or identifying mechanisms that could be involved. There is evidence that estradiol, the principal female sex hormone, reduces hepatic sensitivity to GH, while male sex hormones synergize with the growth-promoting effects of the somatotrophic axis (GH and IGF-1) [36, 37]. Studies involving gonadectomy and sex hormone replacement would be necessary to determine whether these sex hormone actions are in any way related to differential responses of females and males to genetic manipulation of the somatotrophic axis or its targets.

The tendency of mutations interfering with IGF-1 or mTOR signaling to produce an extension of longevity exclusively or preferentially in females contrasts with effects of several pharmacological anti-aging interventions. Testing a variety of drugs for their impact on mouse longevity identified several compounds that – at least at the doses used – either extend longevity only in males or have a more pronounced ‘anti-aging’ effect in males than in females. These drugs include: aspirin; another anti-inflammatory compound, nordihydroguaiaretic acid (NDGA); acarbose, and 17- $\alpha$ -estradiol, a compound with no or very little sex hormone activity [38, 39]. The mechanisms linking the action of these compounds to aging remain to be fully clarified. In fact, sex differences in the effects of pharmacological treatments differ in a fundamental way from sex differences in genetic knockouts, in that they may be due to differential bioavailability of the drug in question due to sex differences in metabolism or clearance. That appears to be the case, for instance, for aspirin and NDGA [38]. By contrast, a gene that is knocked out in one sex is necessarily knocked out in the other as well.

Mechanisms linking the action of the above compounds to aging are unlikely to include altered activity of the somatotrophic axis but may involve some functions modulated by GH, e.g. inflammation and insulin signaling. The reasons for the exclusive or enhanced anti-aging activity of these compounds in males are unknown, but the well-documented sexual dimorphism in the activity of hepatic drug-metabolizing enzymes [40, 41] offers one theoretical possibility. Intriguingly, sex dimorphism in the activity of these enzymes reflects differences between the patterns of pulsatile GH release in males versus females [41, 42].

However, greater effects on male longevity are not a consistent feature of pharmacological anti-aging interventions. The inhibitor of mTOR signaling rapamycin extends longevity in both sexes of mice, but its effect is greater in females [43]. The ability of rapamycin to inhibit mTOR complex 2 and the detrimental impact of RICTOR depletion on male survival may account for this difference [44].

In the context of sex differences in response to a variety of genetic and pharmacological interventions, it is of considerable interest that the sexual dimorphism in the hepatic expression of numerous genes, including those involved in metabolism of steroid hormones and xenobiotics, is virtually eliminated in GH-deficient, long-lived Ames dwarf mice [45]. Similar findings were obtained in ‘little’ (*Ghrhr<sup>lit</sup>*) and in *Ghr<sup>-/-</sup>* mice, which, unlike the Ames dwarfs, have an isolated deficiency of GH signaling [46].

Countless physiological differences between females and males of the same species could contribute to the differences in longevity and in responses to anti-aging interventions discussed in this article. In addition to different levels and ratios of androgenic and estrogenic steroids, sex differences in the levels of adiponectin and leptin, in the distribution of adipose tissue (and the associated differences in its secretory activity), and in the function of the immune system represent some of the obvious ‘candidate mechanisms’ that remain to be explored in this context.

## Conclusions

There are two important conclusions that emerge from the available data. First, women have a robust survival advantage over men, whereas men have a robust health advantage over women. This intriguing paradox deserves more investigation. It would be a major boon to human health if men lived as long as women and if women maintained their health as well as men. Second, because sex differences are broad and unpredictable, inclusion of both sexes in all biomedical studies – regardless of species – is well worth the effort and expense involved. In the USA, since the early 1990s both sexes have been routinely included in National Institutes of Health (NIH)-funded clinical studies. However, similar attention has not been paid to the sex balance in animal studies. These have traditionally been heavily male biased. In May 2014, the NIH issued a policy statement promising to redress this imbalance [47]. We strongly support this effort.

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