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Sex Differences in Lifespan

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SUMMARY

Sex differences in longevity can provide insights into novel mechanisms of aging, yet they have been little studied. Surprisingly, sex-specific longevity patterns are better known in wild animals. Evolutionary hypotheses accounting for longevity patterns in natural populations include differential vulnerability to environmental hazards, differential intensity of sexual selection and distinct patterns of parental care. Mechanistic hypotheses focus on asymmetric inheritance of sex chromosomes and mitochondria. Virtually all intensively studied species show conditional sex differences in longevity. Humans are the only species in which one sex is known to have a ubiquitous survival advantage. Paradoxically, although women live longer, they suffer greater morbidity particularly late in life. This mortality-morbidity paradox may be a consequence of greater connective tissue responsiveness to sex hormones in women. Human females' longevity advantage may result from hormonal influences on inflammatory and immunological responses, or greater resistance to oxidative damage; current support for these mechanisms is weak.

INTRODUCTION

The vast majority of animal species have two sexes and those sexes often differ in many aspects of their biology. Most obviously, males range from a tiny fraction of the size of females to considerably larger and live considerably shorter to substantially longer lives (Austad, 2006; Finch, 1990). Sex differences in longevity can potentially be exploited to help understand mechanisms underlying variation in longevity within a species. Yet these differences remain little studied despite considerable variation among different genotypes of commonly used laboratory species such as *C. elegans* (McCulloch and Gems, 2003), *Drosophila melanogaster* (Malick and Kidwell, 1966), and *Mus musculus* (Austad, 2011).

Surprisingly, much more has been reported about sex differences in longevity among wild populations than among captive populations because numerous long-term field studies have tried to understand the evolutionary forces underlying sex differences in behavior and a host of life history traits such as rates of development, mating systems, and reproductive patterns. Thus we know that female short-finned pilot whales live nearly twice as long as males (Kasuya and Marsh, 1984); and that female African lions, red deer, black-tailed prairie dogs,

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numerous monkeys and apes are also longer-lived than males, although these differences are not as extreme as in the pilot whales (Bronikowski et al., 2011; Clutton-Brock (ed), 2009; Clutton-Brock and Isvaran, 2007). The reputed general pattern among mammals *in nature* is for females to be longer-lived, although this is known for certain in relatively few species. We know there are a number of mammals such as Japanese macaques, savannah baboons, and bannertail kangaroo rats where there is virtually no sex difference (Clutton-Brock and Isvaran, 2007; Waser, 1991). Rarely, male mammals even appear to be the longer-lived sex (see below).

The putative mammalian pattern of greater female longevity has been attributed to a variety of factors. George Williams (1957) hypothesized on theoretical grounds that sex differences in longevity likely reflected evolutionary histories of differences in vulnerability or exposure to environmental hazards due to differences in body size, foraging patterns, or other risky behaviors, which lead to sex differences in the rate of aging itself. Observations of sex-biased survival patterns in various species are consistent with this idea; however, the underlying theory predicting that differences in extrinsic mortality by itself leads to predictable evolved patterns of aging is now seen as incomplete at best (Abrams, 1993; Moorad and Promislow, 2010). Alternatively, sexual selection has been hypothesized to play a major role in longevity differences between the sexes as sexually selected traits are expected to exhibit an evolutionary fitness cost (Promislow, 1992; Promislow et al., 1992). Thus, the prevalence of polygynous mating systems in mammals concomitant with its greater intrasexual selection among males could explain this general pattern if it truly exists (Trivers, 1972). A related, more narrowly defined idea, is that patterns of parental care affect sex differences in in longevity. In support of this idea, females are the longer-lived sex in many primates, but in the few species such as owl and titi monkeys with extensive male parental care, males have a slight longevity advantage (Allman et al., 1998).

There are two additional hypotheses based on asymmetric inheritance. One of these is the heterogametic sex (or unguarded X) hypothesis, which posits that males are shorter-lived sex because they have only a single X chromosome (Trivers, 1985). Specifically, the logic of this hypothesis is that because of females' two X chromosome copies, the phenotypic effect of sex-linked deleterious alleles can be masked by normal alleles on the other X; whereas males have no second X chromosome to compensate for a single bad allele. A second hypothesis also based on asymmetric inheritance is that because mitochondria are only maternally inherited, they will be under selection for optimized compatibility only with the female nuclear genome. Therefore any sexually antagonistic male genes would shorten male life (Tower, 2006).

The sexual selection, parental care, or the heterogametic sex hypotheses each would predict a different sex-longevity pattern in birds. Social monogamy is by far the most prevalent mating system in birds (Promislow et al., 1992; Trivers, 1972). Thus, intrasexual competition is expected to be reduced and extensive male parental care is common so predictions from sexual selection or parental care theories are that there would be little longevity difference between bird sexes. In addition, female birds are the heterogametic sex, so if the heterogametic sex hypothesis is valid, males would be predicted to be the longer-lived sex in birds (Austad, 2011). In fact, there is little reported longevity difference between

the sexes in most bird species studied, but there are a range of species such as the Barnacle Goose, Acorn Woodpecker, and Arabian Babbler in which males are substantially longer-lived than females in the wild (Clutton-Brock and Isvaran, 2007). This is seen in both socially monogamous and socially polygynous species, consistent with the heterogametic sex hypothesis but not with the sexual selection hypothesis.

Most of the studies adduced above are from wild populations. However, longevity differences in wild populations, while evolutionarily informative, may be due to a variety of factors unrelated to sex differences in intrinsic aging rate—the feature of most interest to laboratory and biomedically-oriented biologists. Wild populations could exhibit sex differences in longevity simply because of differential risk-taking behavior, foraging patterns, or mortality due to direct sexual competition. For instance, among birds and mammals, one sex tends to be the dominant disperser -- the one that leaves the natal territory to find a new territory, often at some distance. Dispersal, which involves travelling through unknown terrain, searching for new, available territory is hazardous. In one study, water voles were found to have nearly 100 times the mortality rate during dispersal as when not dispersing (Leuze, 1980). Interestingly, one of the most sex-biased survival differences known among wild mammal populations is seen in Brandt's bat (*Myotis brandti*), the longest-lived mammal species for its body size. Weighing only 7–8 grams, *M. brandti* has been reported to live at least 41 years *in the wild*. All of the 67 individuals of this species known to have survived longer than 20 years have been males (Podlutsky et al., 2005). This could indicate that males of this species are physiologically protected against the ravages of senescence much better than are females. However, it is also possible that the extreme foraging behavior of lactating female bats that must consume up to 50% of their body weight in insect prey daily exposes them to greater risks of predation or energetic stress than males. Thus the longer life of males could be due to differential exposure to environmental hazards rather than intrinsic aging processes. Differences in foraging or risk-taking behaviors are not the only factors complicating longevity differences between sexes. There is also reproduction itself. Reproduction, for instance, is known to be life-shortening in females of a number of species (de Heij et al., 2006; Liker and Szekely, 2005). However, it can also be costly in males, particularly if one includes the cost of male competition (Iliadi et al., 2009; Nussey et al., 2009). Therefore, it is always wise to question whether sex differences in longevity observed in wild population reflect intrinsic differences in the rate of physiological senescence or not. Thus, while studies of sex differences in wild populations can provide important insights into the ultimate causes of aging, they are less useful for understanding the mechanistic underpinnings of sex differences in the intrinsic rate of aging.

If the goal is to understand sex differences in the cellular and molecular physiology of aging, studies of protected populations such as those found as pets or in zoos or research facilities are likely to be more informative. Easy generalizations about certain model species are often found in the literature. For instance, one can find statements that female flies are longer-lived or *C. elegans* hermaphrodites are longer-lived. Similar statements exist concerning sex differences in rodent longevity, sometimes favoring females, other times males. As we show below, such generalizations are seldom justified. Therefore the rest of this review will focus

on what is known about longevity differences in protected populations, focusing mainly on the most thoroughly known and studied laboratory species.

WORMS (*C. elegans*)

Mechanistically, longevity is arguably better understood in the nematode, *C. elegans*, than in any other animal species. Worms have two sexes, males and hermaphrodites. However, virtually everything we know about worm longevity has been from investigations of hermaphrodites only. In the standard N2 laboratory strain of *C. elegans*, which sex is longer-lived depends on culture conditions. Isolated males are 10–20% longer-lived than hermaphrodites, yet when housed in groups, either mixed sex or all male groups, males constantly attempt to mate and the act of mating and mating attempts are such that there is no significant sex difference in longevity (Gems and Riddle, 2000). These results are reminiscent of those seen in Mediterranean fruit flies (*Ceratitis capitata*), in which sex differences in longevity vary depending on housing conditions, diet, and stress level (Carey and Liedo, 1995).

To determine whether this result was a quirk of the N2 strain or more general of the species as a whole, McCulloch and Gems (2003) reared 12 wild isolates that were highly divergent in a variety of traits. In two of these the males appeared sickly through life and were exceptionally short-lived. Excluding these two, in 8 of the 10 other strains males were significantly longer-lived and in the other two there were no significant differences. The mean ratio of male-to-hermaphrodite median longevity in the 10 strains was 1.2. In all 10 of the strains, maximum male longevity exceeded that of hermaphrodites (McCulloch and Gems, 2003). All 12 isolates in this study were androdioecious (having males and hermaphrodites) as opposed to dioecious (with separate males and females). To evaluate whether this pattern might be specific to *C. elegans* or to androdioecious species of free-living soil nematodes like *C. elegans*, seven other species were examined. Three of these were androdioecious like *C. elegans*, the others were dioecious. In 7 of the 8 species, males were the longer-lived sex. Only in one species, the androdioecious *C. briggsae,* were males shorter-lived. Why *C. briggsae* is exceptional is anything but clear. One aspect of its biology that might (or might not) be relevant is that unlike the other androdioecious species, when *C. briggsae* males mate with hermaphrodites, the bulk of the progeny are hermaphrodites rather than a 50:50 mix of males and hermaphrodites as in the other species (McCulloch and Gems, 2003). Although the mechanism(s) underlying these sex differences remain obscure, it is provocative that a *daf-2* mutation in *C. elegans*, which doubles longevity in hermaphrodites more than sextuples it in males (Partridge and Gems, 2002). Understanding these differences seems to be a problem worthy of considerably more investigation.

FRUIT FLIES

The laboratory fruit fly, *Drosophila melanogaster*, has likely been subject to more extensive demographic analysis than any other model organism. There have been few analyses of sex differences in longevity, however. Probably the most extensive analysis focused specifically on sex differences is from Malik and Kidwell (1966). They investigated longevity in 5 isogenic lines and in F_1 hybrids among them. Results were complex and highly dependent

on genotype, mating status, and female fecundity. Generally, isogenic lines were shorter-lived than hybrids and mating decreased longevity of both sexes. The biggest difference favoring males was a male/female ratio of 3.8 in mean longevity. The biggest favoring females was a female/male ratio of 2.3 (Malik and Kidwell, 1966). So sex differences in *Drosophila* lifespan can be extreme. Similar condition-dependence was found in *Drosophila subobscura*, where unmated females live longer than males, but mating shortens female longevity more, so that mated males outlive mated females (Maynard Smith, 1958). More recently, a study of 219 inbred lines (the *Drosophila* Genetic Reference Panel) found that in ~70% of these lines virgin females lived longer virgin males, although there were lines where virgin males lived more than twice as long as virgin females (Arya et al., 2010). Recent work has identified loss of gut integrity as a major cause mortality in *D. melanogaster* (Biteau et al., 2010) and some evidence suggest that sex differences in intestinal stem cell activity may underlie longevity differences in a least some genotypes (Regan et al., 2016).

Interestingly, as with worms, there is also a marked sex difference in the impact of some longevity-enhancing genetic treatments in flies. For instance, reduced signaling in the insulin/IGF pathway enhances longevity substantially in females but has little to no effect on male lifespan (Clancy et al., 2001; Giannakou et al., 2004; Tatar et al., 2001).

While aging in *C. elegans* and *Drosophila* have been extensively studied, sex differences in longevity have not been thoroughly investigated. For *C. elegans* and related species individual housing leads to longer-lived males compared to hermaphrodites whereas group housing abolishes this longevity difference. In flies, which sex is longer-lived depends on genotype, mating status, and female fecundity; under some conditions males are much longer-lived and under others females show significantly greater lifespans. Both systems are well characterized and offer many opportunities for investigations into sex-specific mechanisms that influence aging.

MAMMALS

Females live longer than males in humans and all Old World monkeys and apes for which we have the best data (Austad, 2011; Bronikowski et al., 2011). This appears to be true in both wild and captive populations (Allman et al., 1998; Bronikowski et al., 2011). Yet whether there is a general mammalian pattern of greater female longevity under protected, captive conditions where intrinsic physiological aging dominates mortality patterns, is not known because so few species have been rigorously investigated. What is known about the best described species indicates that all show a substantially different pattern from humans.

Dogs and Cats

One might expect that there would be loads of data on the relative longevity of male versus female house cats and dogs, the most common species of companion animals in the world. Surprisingly, there is relative little information on these two domestic species.

The best data on mortality in cats suggests that females have a small survival advantage. Although two early studies found no significant sex differences, one of those was relatively

small (Bronson, 1981) and in the other age data were truncated at 13 years -- about the median age of death in cats (Egenvall et al., 2009). By far the most comprehensive study (of ~4000 cats) with complete longevity records, median longevity of females was two years or about 15% greater than the longevity of all males (15.0 versus 13.0 years) (O'Neill et al., 2014). In that study as well as in the earlier ones, the impact of neutering on lifespan extension was greater than the impact of sex, however.

For dogs, there is scarcely better information. One small study (N = 287) of laboratory beagles found no significant sex differences in longevity (Albert et al., 1994). However, in a much larger study of thousands of insured Swedish dogs, females were found to be slightly longer-lived (Egenvall et al., 2000). These Swedish results should be interpreted with caution as no information was available on animals at greater than 10 years of age. Again, the most thorough available data from a study of companion dogs with complete lifespans in the United Kingdom, found that after controlling for body weight and pure breed versus mixed breed status, males slightly outlived females by 0.4 years among animals surviving to at least 3 years of age (O'Neill et al., 2013). The median longevity in this study of was 12.1 years, emphasizing why caution is necessary in interpreting the Swedish data. Consistent with an earlier study (Mitchell, 1999), O'Neill and colleagues (2013) also found that neutering increased the longevity of females by about 5.6% but did not the longevity of males.

In summary, information currently available indicates that in intact cats females are slightly longer-lived and in dogs males are slightly longer-lived. For both species though, these results should be considered provisional. Also, breed and reproductive status (intact versus neutered) can alter these simple conclusions.

Laboratory Rats

Until the 1990's laboratory rats were the mammal of choice for most aging studies (Masoro, 1992). Unfortunately, most of those studies focused on males only. However, there have been lifespan studies of laboratory rats of both sexes under a variety of dietary and housing conditions. Most of these studies observed that females live longer than males (Table 1). However in recent decades two sex studies have grown rare, so most of what we know about sex differences in rat longevity stem from the time before specific pathogen free (SPF) animal colonies became the norm. Thus, it is never clear when infectious disease may have had an undue influence on a study's outcome. For instance, McCay's (1935) study of "white" rat longevity observed that female rats lived approximately 66% longer (!) than males when both were fed *ad libitum*. However, compared to other rat studies, the males (but not the females) in that study were exceptionally short-lived. Interestingly, when their diets were restricted in calories, the longevity difference was reversed. In two groups restricted from either weaning or two weeks after weaning, males lived 6% and 8% longer than females. Most studies since that time have found female rats to live longer than males, although the difference is not dramatic, ranging from a female survival advantage of roughly 2% to 15% (Austad, 2011; Sprott and Austad, 1996; Swindell, 2012; Turturro et al., 1999). In particular, the NIA Biomarkers program raised thousands of rats of two inbred strains (F344 and Brown Norway) and one F1 hybrid in both *ad lib*-fed and food-restricted

conditions, including two different diets and found in all cases females lived slightly longer than males. Thus females appear to have a slight survival advantage in multiple rat genotypes under a variety of conditions.

Unlike the other model species mentioned so far, there have been few studies of life-extending interventions in rats – none, in fact, except dietary restriction have been done simultaneously in both sexes. Male response to dietary restriction was greater in 7 of 10 such experiments, including substantial differences in three studies involving the F344 strain alone or hybridized to Brown Norway. The Brown Norway strain by itself had a greater response in females (Sprott and Austad, 1996). These differences are unlikely to be due to chance as they employed sample sizes of approximately 50 animals per sex per group, which is high for rodent studies. However, whether these results are due to the genotype, the details of the diets, or some other idiosyncrasy of husbandry is not clear.

Based on the available data, it appears that female rats are longer-lived than male rats although the difference is not large, the studies are few and were largely completed prior to the availability of specific pathogen free facilities.

Laboratory mice

There has been a great deal of confusion over sex differences in laboratory mouse longevity (Austad, 2011). One can find statements in the literature that males are the longer-lived sex (Ali et al., 2006), that there is no sex difference (Sanz et al., 2007), or that females live longer (Viña et al., 2005). Each of these claims is correct, it turns out – and wrong.

Wild-derived house mice, those whose ancestors have been in the laboratory for only a few generations, exhibit little sex difference in longevity. For instance, in two of three wild-derived populations from the U.S. mainland and two from Pacific islands all kept under identical conditions in the same animal facility, longevity of the sexes differed by 1% or less. In the third however, males lived 19% longer than females (Miller et al., 2002).

In order to determine whether this sort of seemingly arbitrary longevity difference was more consistent in a larger sample of studies, Austad (2011) surveyed 118 survival studies of laboratory mice that included either mean or median longevity for both sexes. These were studies that all used standard laboratory conditions without genetic or dietary manipulations, although they could be inbred, F_1 hybrid, or outbred populations. The studies included a variety of uncontrolled and unknown husbandry differences including but certainly not limited to a range of diets, bedding, housing densities, ambient temperature, and no doubt different pathogen exposure as well. Analysis of these studies clearly showed that mice display no robust or consistent sex differences in longevity. There were substantial sex differences in individual studies though, ranging from males living more than 40% longer to females living more than 70% longer (Storer, 1966). In all, some 65 studies reported that males outlived females, 51 reported that females outlived males, and for the other two studies sex differences were virtually absent.

An obvious suspect to bring some order to this puzzling finding is mouse genetics. All inbred strains of mice or any other species exhibit their own particular idiosyncrasies, of

course. Perhaps sex differences in longevity is one particularly common type of strain idiosyncrasy. However, that turns out not to be the case. There were 29 studies that used C57BL/6 mice and even these studies showed surprising variability. Males lived longer -- up to as much as 20% longer -- in 18 studies; females lived longer, up to nearly 20% longer, in 11 other studies. Other mouse strains that were assessed in multiple studies also showed sometimes longer female lives, other times longer male lives.

Because there were so many uncontrolled variables in comparing all these studies, it was not clear whether the range of sex differences observed was due to discoverable environmental differences or to intrinsic stochasticity. Discovering environmental conditions that favored survival of one sex over the other might be informative for understanding the mechanisms underlying sex differences. To investigate this issue, we wished to examine multiple studies of the same mouse genotype when great care had been taken to standardize the husbandry among studies. Fortunately, this is exactly what has been done with the Interventions Testing Program (Miller et al., 2007).

The Interventions Testing Program (ITP) evaluates compounds that can be administered in food or water for their potential ability to extend mouse longevity. There are several unique features of the program, including that they use genetically heterogeneous mice that are created from the mating of two F1 hybrid lines (CB6F1 × C3D2F1) and they perform all experiments at three sites (Michigan, Texas, Maine) simultaneously. The 3-site design makes standardizing procedures between experiments and across sites especially important. Examining the median longevity of control mice from 3 distinct cohorts at the three sites reveals remarkable consistency, particularly compared to our previous analyses under diverse circumstances (Table 2) (Harrison et al., 2014; Miller et al., 2011; Strong et al., 2008b). In all cohorts at all sites, female mice of this genotype lived longer than males. The mean difference was about 13% in median longevity, with 4% being the smallest difference at any site for one experiment and 19% being the largest difference. A fourth cohort also found a 10% difference in the same direction (Strong et al., 2012).

These consistent results from the ITP indicate that the extreme variability observed in the 118 studies may be resolvable into its causal environmental components. If so, then mice can potentially teach us a lot about the underlying mechanisms of sex differences in longevity.

Perhaps even more surprising than the variability in sex differences in mouse longevity across diverse studies is the sex bias found in many interventions in longevity (Table 3) (Austad and Bartke, 2015). This table only includes studies in which a statistically significant effect was found in only one sex, not in the other. There are a multitude of additional studies in which the effect on one sex is substantially greater than the effect in the other, which we have ignored (e.g. Harrison, et al., 2009). It is not difficult to imagine why dietary or pharmacological studies might differ between the sexes because of differential metabolism or clearance. In fact, this is quite clear with NDGA and aspirin, in which blood levels of the active form of the drugs are significantly higher in one sex compared with the other and that may be the case for the other interventions reported to date by the ITP where, with the notable exception of rapamycin, lifespan is preferentially extended in males (Table

4) (Strong et al., 2008b). It is more difficult to imagine why something like a genetic knockout – presumably just as knocked out in both sexes -- would affect the sexes differently. As with sex differences in unmanipulated mice, there may be a considerable amount to be learned from further investigation of these cases.

In summary, there is no consistent sex difference in mouse longevity, although individual studies can be found to support greater male or female longevity. The conditions favoring survival of one sex over the other are also unknown in mice. However, data from the ITP where conditions and husbandry have been standardized, females median lifespan is consistently great than that of males. These results, coupled with the robust and repeatable sex differences in response to longevity interventions suggest that mice may provide a model for understanding sex differences in aging.

Humans

Consistent sex differences in longevity, robust across diets, mating patterns, and environmental vagaries, have not been seen in any of the species discussed so far. However, in humans robust sex differences do exist. Indeed, the sex difference in longevity may be one of the most robust features of human biology (Austad, 2011).

Many orders of magnitude more longevity data are available for humans than for any other species, but those data are not always reliable. For instance, according to official United Nations data from 1990, residents of Malawi, where life expectancy was only about 40 years, survived better later in life than residents of Japan, the longest-lived country in the world (Austad, 1997). Even with these uncertainties in data quality, however, 176 of the 178 countries, islands, and principalities for which the United Nations currently keeps records have a clear female longevity advantage (http://unstats.un.org/unsd/demographic/products/dyb/dyb2014.htm).

The best source of historical and current human mortality data is the Human Mortality Database (http://www.mortality.org/) which currently has information on 38 countries over periods with particularly reliable data. For instance, complete life tables for both males and females are available from Sweden and France since 1751 and 1816, respectively, but from Japan and Russia only since 1947 and 1959, respectively. Given this high data quality, it is impressive that for all 38 countries for every year in the database, female life expectancy at birth exceeds male life expectancy. The robustness of this pattern is even more apparent when considering that in very early life (birth to age 5) female survival is uniformly better across years and across countries as is later life survival (life expectancy at age 50) (Austad and Bartke, 2015). Indeed, using data from the Gerontology Research Group (http://www.grg.org/Adams/Tables.htm) to examine sex differences in the oldest of the old, women comprise 90% of supercentenarians (individuals living to 110 years or longer), although the mean age among supercentenarians is comparable between the sexes ($\bar{X}$ = 111.5 vs 111.3, females and males respectively).

A particularly vivid example of female survival advantage can be seen in the demographic history of Iceland, a small genetically homogeneous country, historically beset by multiple catastrophes such as famine, flooding, volcanic eruptions, and disease epidemics (Andreeva,

2008). For Icelandic birth cohorts spanning the mid-19th to early 20th century (the latest complete cohort data available), life expectancy at birth fell to as low as 21 years during catastrophes and rose to as high as 69 years during good times. Yet in every year, regardless of food availability or pestilence, women at the beginning of life and near its end survived better than men (Figure 1). Although the sex bias in survival has existed for as long as reliable demographic information is available, it widened for mid- to late life survival in the very late 19th and early 20th centuries as a consequence of a rapid increase in cardiovascular disease in men likely due to food superabundance and sex differences in smoking behavior (Beltran-Sanchez et al., 2015).

It used to be thought that women's survival advantage began at conception and was robust *in utero* as well (Austad, 2011). However, extensive new research on prenatal mortality has now discovered that the advantage begins only several weeks prior to birth (Orzack et al., 2015). Orzak et al (2015) compiled data on almost 140,000 embryos aged 3–6 days conceived under assisted reproductive technologies (ART) and determined that 50.2% were male. Of these embryos, 60% had karyotypic abnormalities, consistent with the data reported from inspections of spontaneous abortions. Of those embryos with abnormalities, 50.9% were male, a statistically significant difference but perhaps not biologically significant. While it can be argued that ART is not the same as natural fertilization, the sex ratio at birth of babies conceived by ART and natural fertilization does not differ (Orzack et al., 2015). Orzack et al (2015) used additional data from studies of abortion, chorionic villus sampling and amniocentesis results and determined that male-biased mortality predominated through week 2, followed by female biased deaths for the next 4 months, succeeded by period of no sex bias and finally returning to male biased mortality during the final 5 weeks prior to birth.

As should be obvious by now, women are not simply resistant to one or two major causes of death. They are less likely to succumb to most of the major causes of death. Of the 15 top causes of death in the United States in 2013, women died at a lower age-adjusted rate of 13 of them, including all of the top 6 causes (Table 5). For one cause, stroke, there was no sex bias, and for one other, Alzheimer's disease, women were more at risk (Xu et al., 2016).

The Mortality-morbidity Paradox—One of the most puzzling aspects of human sex difference biology, something that has no known equivalent in other species, is that for all their robustness relative to men in terms of survival, women on average appear to be in poorer health than men throughout adult life. This is the mortality-morbidity paradox. In developed Western societies where copious data are available, women make more doctor visits, take more medications, miss more days of work for health reasons, and spend more days in hospitals than men (Christensen et al., 2009; Macintyre et al., 1999; Verbrugge and Wingard, 1987). One possible explanation of this unexpected pattern is that women are more attentive to physical discomfort and illness than men and are more willing to seek medical attention when they experience them (Macintyre et al., 1999). However, the empirical evidence to support this hypothesis is uneven and often contradictory. Moreover, it turns out that the mortality-morbidity paradox is not confined to Western societies where medical help is easily available, nor is it confined to self-reported data. Higher prevalence of women's physical limitations in later life has also been reported in Bangladesh, China, Egypt,

Guatemala, India, Indonesia, Jamaica, Malaysia, Mexico, the Philippines, Thailand, and Tunisia (Rahman et al., 1994; Wheaton and Crimmins, 2016). Objective measures of sex differences in physical function batteries involving muscle strength, responsiveness, and balance have also shown a female disadvantage in the United States, Taiwan, Korea, China, Indonesia, and even among the Tsimane, an indigenous non-technological, foraging-horticultural group living in eastern Bolivia (Wheaton and Crimmins, 2016).

What might explain this paradox? There are several plausible hypotheses. The first is that the mortality pattern itself might explain the morbidity pattern (Manton et al., 1995). The so-called mortality-selection hypothesis posits that precisely because men die at higher rates than women throughout life, surviving men are likely to be more physically robust because those who were not would have died. Consistent with this idea are observations such as the fact that men die at a higher age-adjusted rate than women from heart diseases, but morbidity associated with heart disease is greater in women (Wingard et al., 1989). Interestingly, if valid, this hypothesis implies that in any species with a significant sex bias in mortality, we should also observe a mortality-morbidity paradox. The fact that the same pattern has been reported in no other species may reflect that it is a unique human trait or that we do not have the refined data on later life health in other species that we do in humans. However, in the few studies that have attempted to account for mortality selection statistically, a sex difference in morbidity still remains (Doblhammer and Hoffmann, 2009).

A less general explanation for the mortality-morbidity paradox is that it has to do with the particular health problems to which humans are prone in later life. It may really be a human-specific phenomenon. Women are well-known to suffer more joint and bone problems such as osteoarthritis, osteoporosis, and idiopathic back pain than men (Pinn, 2006). Back and joint pain from arthritis is not only more common, it tends to be more severe among women (Crimmins, 2004; Verbrugge, 1995; Wan et al., 2005). Chronic pain from such conditions cannot only limit activity but can also lead sufferers to seek medical help – both features of greater female morbidity -- but can also have more far-reaching secondary effects from sequelae such as chronic sleep deprivation and stress. Thus it is tempting to hypothesize that the sex difference in morbidity is largely due to the more general phenomenon of women's greater susceptibility to connective tissue maladies. Connective tissue in humans at least are known to be particularly responsive to female hormones (Karasik and Ferrari, 2008; Roman-Blas et al., 2009). Sex differences in joint health are not confined to older ages. Women are also considerably more prone to anterior cruciate ligament injury than men during athletic activities (Heitz et al., 1999; Prodromos et al., 2007). To be wildly speculative, perhaps this greater connective tissue responsiveness to hormones may be a side-effect of the necessary pelvic ligament responsiveness to hormones during pregnancy and childbirth (Reese and Carey, 2015). In any case, humans are currently the only species in which the mortality-morbidity paradox has been observed.

MECHANISMS OF SEX DIFFERENCES IN LONGEVITY

Ultimately, of course, we would like to understand the fundamental cellular and molecular mechanism(s) that account for sex differences in longevity. In every species mentioned above except for humans, sex differences appear to be conditional on some known, and

some unknown, factors. For worms, and flies, mating itself may reverse or eliminate sex differences. Genetic factors also affect sex differences as shown by the fact that females live longer in ~70% of the inbred strains in the Drosophila Genetic Reference Panel whereas ~30% of the strains males live longer (Arya et al., 2010). Beyond mating history and genetics, there are also obviously unknown environmental factors at work as well. What, for instance, causes females of a single, widely-used mouse genotype, C57BL/6, to live more than 30% longer than males in one study (Cheney et al., 1980) and males to live consistently 10% or more longer in repeated survival studies from another laboratory (Tanaka et al., 2000)?

Although there has been considerable theorizing, there have been relatively few studies specifically addressing mechanisms of sex differences in longevity. These few mechanistic studies have focused most often on humans or laboratory rodents. The two physiological systems most often invoked are the endocrine and immune systems. These of course are known to be related to one another in that sex hormones are well-known to affect immune response (Gubbels Bupp, 2015). As was previously noted, lack of mating or sterilization has been repeatedly reported to lengthen life in numerous species, including all species discussed here, suggesting that reproductive hormones may be partially explanatory. In humans in particular, historical records have been examined in Korea indicating that males lacking testosterone, i.e. castrated males, lived 15–20 years longer than intact men of the same socioeconomic strata (Min et al., 2012). By itself, this study would not be particularly compelling as historical records can be mistaken or misleading, but 20th century records on institutionalized men who has been castrated found a surprisingly similar result (Hamilton and Mestler, 1969).

Now that we know that human females survival better than males even in the first few years after birth as well as throughout later life (Austad and Bartke, 2015) (Figure 1), some thought ought to be given to the impact of early life hormone exposure on both early and later life health. In addition to dramatic hormonal differences after puberty, male fetuses exhibit a surge of testosterone during sexual differentiation *in utero* (Winter et al., 1977) and both sexes experience activation of the hypothalamic-pituitary-gonadal axis in the first few months of postnatal life (Andersson et al., 1998). The increasing realization that early life events can have manifold later life health impacts make the examination of early life hormonal profiles of particular interest (Bartke et al., 2016; Brakefield et al., 2005; Sonntag et al., 2005). Assuming that the survival advantage is fairly general to female mammals (something that is still unknown), then the anti-oxidant (Mann et al., 2007; Stice et al., 2009) and anti-inflammatory (Benedusi et al., 2012; Villa et al., 2015) properties of estrogen seem like one obvious place to look for an explanation. Both oxidative damage and chronic low-grade inflammatory activation in later life have been implicated in aging (Barja, 2004; Finch, 2007; Ku and Sohal, 1993). Greater steady-state oxidative damage to DNA has been found in peripheral blood leukocytes in men compared to women (Proteggente et al., 2002). Similar sex differences have found in mtDNA damage from tissues of Wistar rats in which female life expectancy exceeded male life expectancy by 16% (Borras et al., 2007). In this rat study, mitochondria from females were observed to produce more pro-oxidants and have higher antioxidant enzyme levels than male mitochondria. The impact of estrogen as a

causative agent was verified by ovariectomizing the rats and noting that pro-oxidant levels rose, then fell again when exogenous estrogen was added back.

In addition to oxidative stress, the endocrine impact on immunity and inflammation also should not be ignored. Although there have been numerous studies assessing various aspects of immune responsiveness in adult humans in which females have often proven to have more robust responses (Ferguson et al., 2013; Gubbels Bupp, 2015; Oertelt-Prigione, 2012), there have been few such studies in infants. Yet given the early survival differences between the sexes, if differential immune competence could be affecting survival differences, then studies of infants might seem warranted.

CONCLUSIONS

A thorough examination of sex differences in longevity in the animal species we know most about has revealed that it is seldom warranted to generalize in claiming that female (or male) worms, flies, dogs, mice, or rats are the longer-lived sex. In virtually every case, it is condition-dependent. Thus in the search for mechanisms underlying sex differences we need to be aware of, and even take advantage of, the conditions favoring one sex versus the other. In some cases these conditions are known, in others such as with mice, the conditions remain obscure. However as single mouse genotypes sometimes exhibit greater male longevity, sometimes greater female longevity, this offers an excellent system to investigate sex differences further if the predisposing conditions can be identified. The one species with copious data indicating that greater female longevity is virtually universal is humans. The recent discovery that female survival advantage begin at (or perhaps slightly before) birth suggests that investigation of the mechanisms facilitating this early survival difference may yield insight into life-long differences as well.

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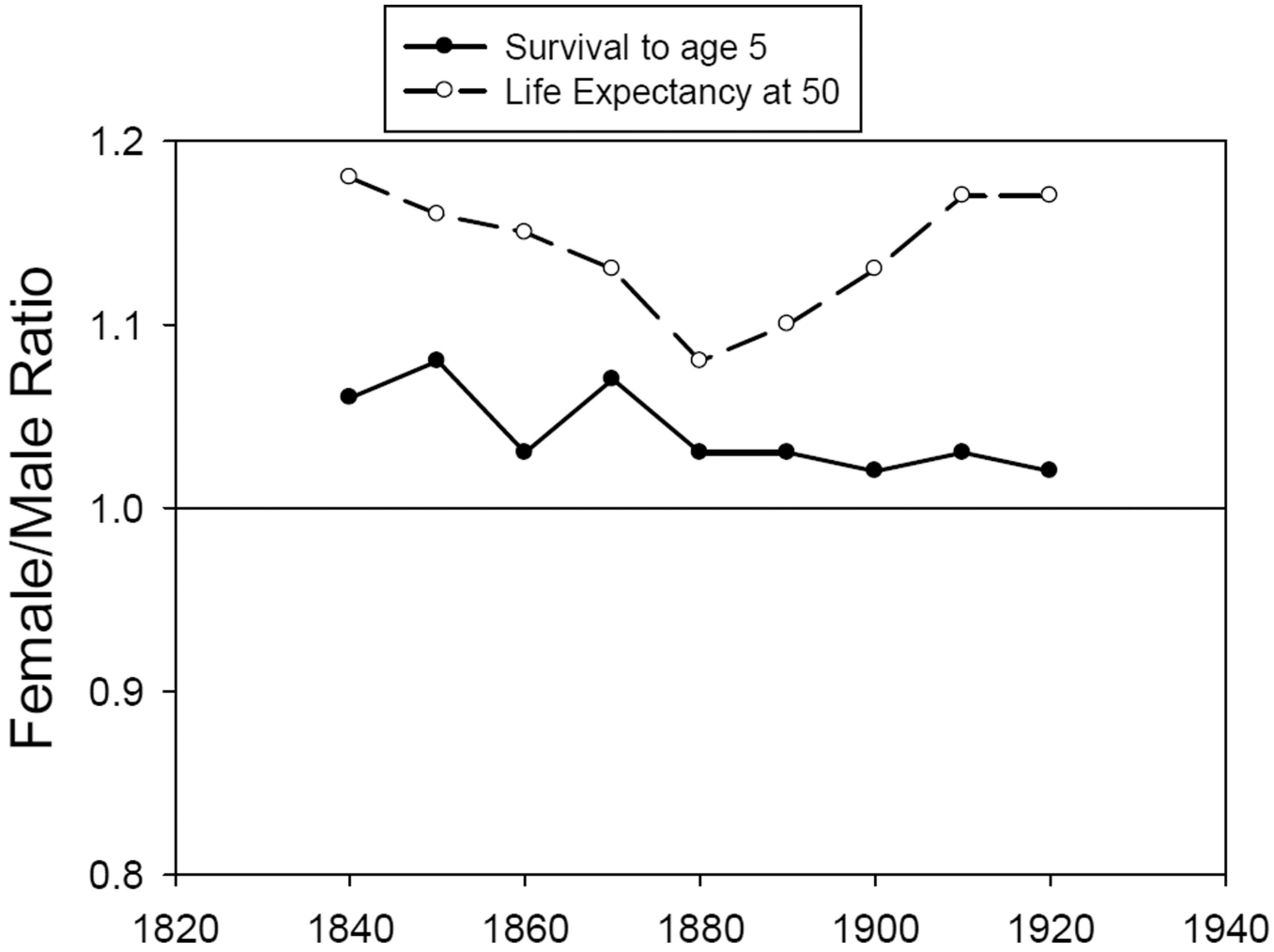

Figure 1.

Survival to age 5 and life expectancy at age 50 in Icelandic population cohorts born between 1840 and 1920. Note that female survival surpassed male survival in every year at both the beginning of life and later in life. Source: Human mortality database.

Table 1

Sex differences in laboratory rat (*Rattus norvegicus*). Longevity in months.

Study	Strain/Type	Male longevity*	Female longevity*	M/F	Male DR longevity*	Female DR Longevity*	DR M/F	Male DR Effect Size (%)	Female DR Effect Size (%)
McCay *et al.*, 1935	"white"	16.1	26.7	0.60	27.3	25.8	1.06	70	−3
McCay et al., 1935	"white"	16.1	26.7	0.60	29.8	27.5	1.08	85	3
Carlson & Hoelzel, 1946	Wistar	20.4	22.9	0.89	22.8	24.4	0.93	12	7
Gilbert, *et al.*, 1958	Wistar	24.7	23.1	1.07	28.1	30.0	0.94	14	30
Berg & Simms, 1961	Sprague-Dawley	25.0	30.3	0.83	33.3	>40.0	<0.83	33	>33
Nolan, *et al.*, 1972	Albino	23.5	25.2	0.93	30.8	29.1	1.06	32	15
Sprott & Austad, 1996	F344	24.0	27.5	0.87	29.2	30.7	0.95	22	12
Sprott & Austad, 1996 (diet 2)	F344	23.3	26.3	0.89	29.7	30.2	0.98	27	15
Sprott & Austad, 1996	BN	28.8	30.3	0.95	33.1	37.5	0.88	15	24
Sprott & Austad, 1996	F344BNF1	31.0	32.3	0.96	40.6	43.3	0.94	31	34

*Mean or median, whichever was available. If both were available, mean was used.

Table 2

Median longevity in days of *ad lib*-fed UM-HET3 mice in multiple studies from three sites under rigorously standardized conditions.

	TJL			UM			UT			
	Males	**Females**	**F/M**	**Males**	**Females**	**F/M**	**Males**	**Females**	**F/M**	**Mean F/M**
Cohort 1	781	858	1.10	876	909	1.04	739	876	1.19	1.11
Cohort 2	800	889	1.11	851	891	1.05	780	843	1.08	1.08
Cohort 3	807	918	1.14	925	949	1.03	704	981	1.39	1.19
Mean	796	888	1.12	884	916	1.04	741	900	1.21	1.13

The three sites were TJL = The Jackson Laboratories, UM = University of Michigan, UT = University of Texas Health Science Center San Antonio.

Cohort 1 from Strong, et al. (2008), Cohort 2 from Miller, et al. (2011), Cohort 3 from Harrison, et al., (2014)

Table 3

Studies finding single sex longevity effects in response to various interventions.

Genetic background	Intervention	Females	Males	Source
	GENETIC			
129/Sc	IGF-1R +/−	Increased	NS	(Holzenberger et al., 2003)
C57BL/6J	IGF-1R +/−	Increased	NS	(Bokov et al., 2011)
C57BL/6J	IR +/−	NS	Increased	(Nelson et al., 2012)
C57BL/6	IRS1 −/−	Increased	NS	(Selman et al., 2008)
C57BL/6	Protein Kinase A RIIβ −/−	NS	Increased	(Enns et al., 2009)
Mixed (C57BL/6J & BALB/cOlaHsd)	Sirt6 over-expression	NS	Increased	(Kanfi et al., 2012)
C57BL/6	S6K1−/−	Increased	NS	(Selman et al., 2009)
C57BL6/129S5	mtor+/−; mlst8/−	Increased	NS	(Lamming et al., 2012)
	PHARMACOLOGICAL			
UM-HET3	NGDA	NS	Increased	(Strong et al., 2008a)
UM-HET3	Aspirin	NS	Increased	(Strong et al., 2008a)
UM-HET3	17-α-Estradiol	NS	Increased	(Harrison et al., 2014)
	DIETARY			
GHRKO	30% DR	Increased	NS	(Bonkowski et al., 2006)

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Table 4

Results from the Intervention Testing Program. With the exception of rapamycin, interventions preferentially increased longevity in male mice.

Compound	Amount in Food	Age at treatment initiation	Females (Median; at 90% mortality)	Males (Median; at 90% mortality)	Source
Aspirin	20 ppm	4 months	0; 0	Increased 8%; 0	(Strong et al., 2008a)
NFP	200 ppm	4 months	0; 0	0; 0	(Strong et al., 2008a)
NDGA	2500 ppm	9 months	0; 0	Increased 12%; 0	(Strong et al., 2008a)
4-OH-PBN	315 ppm	4 months	0; 0	0; 0	(Strong et al., 2008a)
CAPE	30 ppm	4 months	0; 0	0; 0	(Harrison et al., 2009)
CAPE	300 ppm	4 months	0; 0	0; 0	(Harrison et al., 2009)
Enalapril Maleate	120 ppm	4 months	0; 0	0; 0	(Harrison et al., 2009)
Rapamycin	14 ppm	20 months	Increased 13(38)%*	Increased 9(28)%*	(Harrison et al., 2009)
Rapamycin	14 ppm	9 months	Increased18%; Increased 13%;	Increased 10%; Increased 16%;	(Miller et al., 2011)
Simvastatin	12 ppm	10 months	0; 0	0; 0	(Miller et al., 2011)
Simvastatin	120 ppm	10 months	0; 0	0; 0	(Miller et al., 2011)
Resveratrol	300 ppm	12 months	0; 0	0; 0	(Miller et al., 2011)
Resveratrol	1200 ppm	12 months	0; 0	0; 0	(Miller et al., 2011)
Resveratrol	300 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Oxaloacetic acid	2200 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Green tea extract	2000 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Curcumin	2000 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Medium chain triglyceride oil	60000 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
17α-Estradiol	4.8 ppm	10 months	0; 0	Increased 12%; 0	(Harrison et al., 2014)
Methylene Blue	28 ppm	4 months	0; 0	0; 0	(Harrison et al., 2014)
Acarbose	1000 ppm	4 months	Increased 5%; Increased 9%	Increased 22%; Increased 11%	(Harrison et al., 2014)
Rapamycin_LoPhase II	4.7 ppm	9 months	Increased 16%; Increased 5%	3%; 0	(Miller et al., 2014)

Compound	Amount in Food	Age at treatment initiation	Females (Median; at 90% mortality)	Males (Median; at 90% mortality)	Source
Rapamycin_Mid Phase II	14 ppm	9 months	Increased 21% Increased 11%	Increased 13%; Increased 8%	(Miller et al., 2014)
Rapamycin_HiP hase II	42 ppm	9 months	Increased 26%; Increased 11%	Increased 23%; Increased 8%	(Miller et al., 2014)
NDGA Lo_Phase II	800 ppm	6 months	--**	Increased 8% (median)**	(Harrison et al., 2014)
NDGA Med_Phase II	2500 ppm	6 months	--**	Increased 10% (median)**	(Harrison et al., 2014)
NDGA Hi_Phase II	5000 ppm	6 months	0; --**	Increased 9% (median)**	(Harrison et al., 2014)

Table 5

Sex differences in age-adjusted death rates for the 15 leading causes of death in the United States in 2010 (from Xu, et al., 2016)

Rank	Cause	Percent of total deaths	M/F age-adjusted death rates
1	Diseases of heart	23.5	1.6
2	Cancer	22.5	1.4
3	Chronic lower respiratory disease	5.7	1.2
4	Accidents	5.0	2.0
5	Cerebrovascular diseases (stroke)	5.0	1.0
6	Alzheimer’s disease	3.3	0.7
7	Diabetes mellitus	2.9	1.5
8	Influenza and pneumonia	2.2	1.3
9	Chronic kidney diseases	1.8	1.4
10	Suicide	1.6	3.7
11	Septicemia	1.5	1.2
12	Chronic liver disease	1.4	2.0
13	Hypertension	1.2	1.1
14	Parkinson’s disease	1.0	2.3
15	Pneumonitis	0.7	1.8