Sex and Life Expectancy

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ABSTRACT

Background: A sexual dimorphism in human life expectancy has existed in almost every country for as long as records have been kept. Although human life expectancy has increased each year, females still live longer, on average, than males. Undoubtedly, the reasons for the sex gap in life expectancy are multifaceted, and it has been discussed from both sociological and biological perspectives. However, even if biological factors make up only a small percentage of the determinants of the sex difference in this phenomenon, parity in average life expectancy should not be anticipated.

Objective: The aim of this review is to highlight biological mechanisms that may underlie the sexual dimorphism in life expectancy.

Methods: Using PubMed, ISI Web of Knowledge, and Google Scholar, as well as cited and citing reference histories of articles through August 2012, English-language articles were identified, read, and synthesized into categories that could account for biological sex differences in human life expectancy.

Results: The examination of biological mechanisms accounting for the female-based advantage in human life expectancy has been an active area of inquiry; however, it is still difficult to prove the relative importance of any 1 factor. Nonetheless, biological differences between the sexes do exist and include differences in genetic and physiological factors such as progressive skewing of X chromosome inactivation, telomere attrition, mitochondrial inheritance, hormonal and cellular responses to stress, immune function, and metabolic substrate handling among others. These factors may account for at least a part of the female advantage in human life expectancy.

Conclusions: Despite noted gaps in sex equality, higher body fat percentages and lower physical activity levels globally at all ages, a sex-based gap in life expectancy exists in nearly every country for which data exist. There are several biological mechanisms that may contribute to explaining why females live longer than men on average, but the complexity of the human life experience makes research examining the contribution of any single factor for the female advantage difficult. However, this information may still prove important to the development of strategies for healthy aging in both sexes. (*Gend Med.* 2012;9:390–401)

Key words: biology, health, life expectancy, sex.

INTRODUCTION

Considered an extraordinary constant of human achievement, life expectancy has increased by approximately 3 months per year for the past 160 years.[1] This trend of increased longevity is observed in both men and women, but a strong sexual dimorphism exists in absolute human life expectancy. Women exhibit greater life expectancy than men,[2–4] and this sexual dimorphism holds true at all time periods[5] and in almost every country, depending on which of the current reports is referenced.[6] According to the World Health Organization (WHO), however, an examination of 193 countries for which data was available (**Figure 1A**)[7] reveals that the gap in life expectancy between sexes is narrowing even though females still continue to live longer than males.

Technological advances in health care have led to treatments for illness and disease that would have previously been debilitating or fatal (eg, hepatitis, polio, and smallpox). Likewise, advances in both proactive and reactive health-care strategies allow early detection and more effective treatment of many illnesses, whereas pharmaceutical advance-

Accepted for publication October 11, 2012.
http://dx.doi.org/10.1016/j.genm.2012.10.001
1550-8579/$ - see front matter

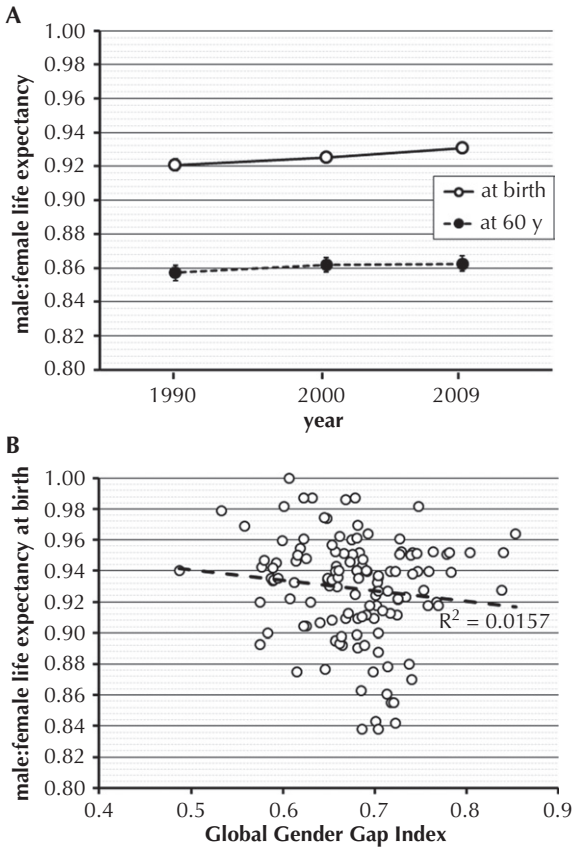

Figure 1. Trends in sex differences in global life expectancy. (A) Male-to-female ratio of life expectancy at birth in 193 countries. Data were obtained from World Health Organization country statistics reported in the years 1990, 2000, and 2009 and are presented as global means and SE. (B) Global male-to-female ratio of life expectancy at birth versus the Global Gender Equality Index in 131 countries for which data were available for both indices. Life expectancy values were taken from the World Health Organization country statistics most recent report (2009), whereas the Global Gender Gap index is a standard developed by the World Economic Forum based on sex equity under educational, economic, political, and health criteria.[7] A value of 1.00 would represent complete parity between men and women. As such, the difference between 1.00 and the reported number represents the sex gap. A bivariate correlation was performed using IBM SPSS Statistics Version .20 between the Gender Gap Index and male:female life expectancy at birth. A significant correlation was not observed. Line of best fit and R^2 are displayed for reference.

ments increase the quality of life of individuals living with chronic disease. These developments may be responsible for the significant increases in life expectancy, improvements in mortality, and a greater quality of life observed over time. The female advantage in life expectancy is obviously multifaceted, and this complexity becomes even more apparent when the Global Gender Gap Index (GGI) is examined. Globally, there is no correlation between the educational, economic, political, and health criteria that make up the GGI and the male-to-female ratio of life expectancy at birth (**Figure 1B**). In nearly every country, a sex gap in life expectancy exists.

Recently, it was predicted that in parts of the United Kingdom, a nation that ranks high on the GGI (ie, closer to parity) and low in female mortality, males born in the year 2000 who reach the age of 30 will live as long as their female counterparts.[8] These predictions were primarily based on the convergence of life expectancy trends over the past several decades and theorized to be mostly due to modifiable societal factors such as a male smoking habits and females participating in other "unhealthy male behaviours."[8] However, it is important to note that women report greater problems in accessing health care at all ages,[9] have higher normalized levels of body fat,[10] and report lower lifetime activity levels compared with males at all ages in nearly every country, including the United Kingdom.[11] Consequently, although it would be unwise to instead suggest that biological mechanisms alone are responsible for the female advantage in life span, clearly human males and females differ in this regard. Here we argue that females possess a biological advantage in longevity that is likely to continue as long as the sexes exist.

FEMALES POSSESS A GENETIC ADVANTAGE AT CONCEPTION

Although not ubiquitous among animal species, the sexual dimorphism in longevity tends to favor the homogametic sex (eg, human females or avian males) over the heterogametic sex (eg, human males or avian females).[12] Human males receive an X chromosome from their biological mother and a Y chromosome from their biological father, whereas females receive an X chromosome from both par-

ents. This chromosomal constitution is primarily responsible for biological sex, but has implications in the viability of the human organism. In females, shortly after conception, 1 X chromosome is randomly inactivated in each cell such that a 50:50 distribution between cells expressing each chromosome typically results.[13]

X chromosome inactivation typically protects against a double dose of X chromosome gene expression in females; however, it also protects females against disadvantageous genes on 1 X chromosome. Potentially unfavorable genes on 1 X chromosome will only be expressed by half of the cells in the female body. In contrast, all of the cells in a male will be affected by an unfavorable gene on the single X chromosome. Indeed, the female biological advantage is most notable in infant mortality in which the death rates are higher for male infants because they are more likely to experience the consequences of infection and congenital disorders.[14]

Moreover, as females age, there is a progressive skewing of X chromosome inactivation toward a predominant single cell line.[15] Ratios >90:10 have been observed in older females.[16] Consequently, inactivation of the disadvantageous X chromosome in 1 cell line affords females the ability to best defend against the physiological stresses of life and aging, thereby providing a growth or survival advantage over the heterogametic male. Although evidence of progressive skewing of X inactivation has been observed in other mammals,[17,18] evidence in humans is minimal, and more research is necessary to determine whether inactivation patterns across the life span actually confers a health-based advantage.

Nonetheless, the genetics of the female life expectancy advantage offers an area of novel discovery. For example, a recent review outlined sex and species differences in telomere biology and life span.[19] In brief, telomere attrition (ie, the progressive decrease in chromosomal length that occurs with cellular division/replication and damage) is correlated with shorter life spans of several species of animals.[19] In humans, adult males exhibit shorter telomeres than females.[19] This is not the case in all organisms, but it is not difficult to imagine the implications. Further, genetic sex differences are not limited to the nuclear genome. Mitochondria are inherited from human mothers only, and, consequently, it has been proposed that the mitochondrial genome is optimized for function with the female genome through natural selection acting predominantly on the mitochondrial-nuclear genome interactions in females.[20] This optimization of mitochondrial "fitness" in female cells could confer a life span advantage given that mitochondrial dysfunction has been implicated in aging[21] and disease such as cancer[22] and cardiovascular and neurodegenerative diseases.[23]

Even if only a small genetic advantage exists in X chromosome dose/activation, telomere attrition, and/or mitochondrial inheritance/selection, it is unlikely that human life expectancy will reach sexual parity until the biological limits of life expectancy are attained.

SEX HORMONES DETERMINE SEX AND ALTER THE BIOLOGICAL LANDSCAPE OF MEN AND WOMEN

After conception and the genetic determination of sex, the primary modulators of sexual development are the endogenous sex hormones testosterone and estrogen. Because women live longer than men, it could be theorized that it is the relative concentration of these hormones that may be responsible for the gap in life span. However, estrogen supplementation concomitant with the inhibition/removal of endogenous androgen (testosterone) production confers neither a benefit nor detriment in mortality or morbidity.[24] The same is true of female-to-male transsexuals in whom androgen is supplemented.[24]

The reproductive theory of aging suggests that a dysfunctional hypothalamic-pituitary-gonadal (HPG) axis, and hence dysregulated sex hormones, is associated with increased mortality in both men and women. Indeed, women who maintain reproductive function later in life are more likely to live longer.[25] However, hormonal balance across the life span is difficult to ascertain in a single individual, and replacement of either estrogen in females or testosterone in males to mimic natural hormone fluctuations across the life span is difficult at best. Nonetheless, the overarching influence of the sex hormones on

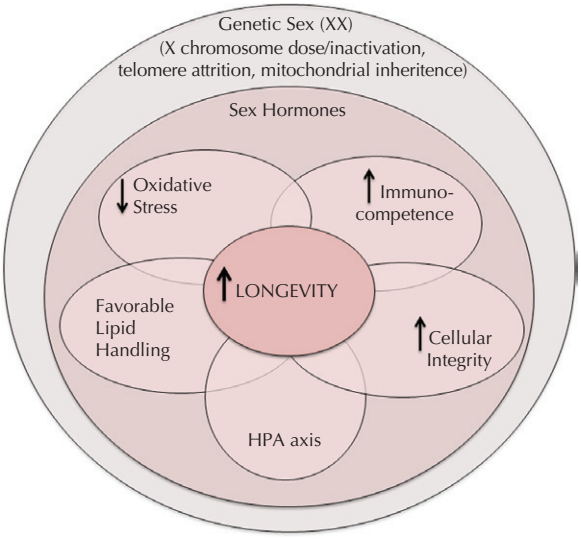

Figure 2. Contributing factors to the female biological advantage in life expectancy. Genetic sex (ie, chromosomal constituency) identifies biological sex, but it is the hormonal milieu and local factors that ultimately determine gonadal and phenotypic sex. Nonetheless, random and selective X chromosome silencing provide females a genetic advantage by which dysfunctional or advantageous genes can be repressed or expressed, respectively, in female tissue. Further, recent hypotheses include reduced telomere attrition and maternal mitochondrial inheritance as genetic components contributing to the female life expectancy advantage. After conception, different circulating concentrations of sex hormones (ie, estrogen, progesterone, and testosterone) underlie many of the physiological differences between the sexes. Hormonal influences on female biology at the organizational level in early fetal and childhood development, as well as after puberty, lead to favorable differences in immune function, oxidative stress and antioxidant status, lipoprotein metabolism, lipid storage and metabolism, the hypothalamic-pituitary-adrenal (HPA) axis stress response, and the ability of female cells to maintain integrity in the face of several stresses. A combination of these factors may be a component of the female life expectancy advantage.

biological health cannot be discounted (**Figure 2**). For example, there is a clear sex- and hormone-based difference in bone health across the life span. Estrogen and testosterone are important regulators of bone mineral density in men and women. After menopause, when circulating estrogen concentrations decrease dramatically, there is a concomitant reduction in bone mineral density in females. Males, in contrast, experience a much more gradual decrease in testosterone and do not exhibit the same loss of bone mineral density. Not surprisingly, women are almost twice as likely to experience bone fractures because of falls. However, even this phenomenon is complex as far as life expectancy is concerned. Women are no more likely to experience the negative consequences of peripheral (eg, wrist, arm, leg) fractures than men, and, in fact, in different parts of the world, men exhibit higher mortality after fractures than women.[26,27]

FEMALES FAVORABLY STORE AND METABOLIZE LIPIDS

The relative amount and storage location of adipose tissue is an outwardly distinguishable difference in the physiological comparison of males and females. There is abundant research that shows that an excessive amount of adipose tissue is related to an increased risk of all-cause and cause-specific mortality.[28] Further, adipose tissue is known to secrete adipokines, which have important effects on systemic metabolism.[29] Given that, after correcting for body mass index, women have greater adipose stores than men,[10] it would be a straightforward assumption that females carry the greater risk. Fortunately for females, this assumption does not hold true, as it is apparent that the storage location of adipose tissue is more important than the amount of tissue itself.

Men tend to store more fat in the abdominal region, and women tend to store more fat in the hips, thighs, and buttocks.[30] Likewise, women tend to have greater amounts of subcutaneous fat, whereas men are more likely to accumulate visceral adipose tissue at nearly all levels of body fatness.[31] Visceral fat, stored in the abdominal cavity around organs, has been implicated in a number of diseases including metabolic syndrome,[32] coronary artery disease,[33] obstructive sleep apnea,[34] ischemic heart disease,[35] and endothelial dysfunction.[36] The increased risk of disease associated with visceral fat has also been found in persons of normal weight.[37]

Two prominent hypotheses as to why excess visceral fat confers more negative consequences

than excess subcutaneous fat implicate the differing anatomic locations and secretions of the 2 tissues. Visceral fat stores have been shown to secrete greater amounts of inflammatory interleukin-6,[38] vascular endothelial growth factor,[39] plasminogen activator inhibitor-1,[39] and C-reactive protein.[40] The combined result of these secretions is an increased incidence of metabolic syndrome,[37] systemic inflammation,[38] and greater mortality in men and women.[41] The implications of the difference between adipose tissues become more severe when the location of visceral fat is considered. Visceral fat accumulates around the organs in the abdominal cavity and is subject to an increased rate of lipolysis due to a greater amount of β-adrenergic receptors and less α-adrenergic inhibition.[42] An increase in free fatty acid (FFA) release from these tissues causes an influx of FFA to the liver where it circulates immediately through the portal vein. The increased FFA exposure has been shown to increase prehepatic insulin production and to decrease hepatic insulin clearance, exposing the liver to higher concentrations of insulin, leading to peripheral hyperinsulinemia and reduced insulin sensitivity.[43] Further, visceral adiposity is associated with both hepatic and peripheral insulin resistance regardless of sex.[44] Decreased insulin sensitivity is a risk factor and symptom of type 2 diabetes, which leads to a lower quality of life and possible future complications.

Considering men tend to store greater amounts of fat in the abdominal region and are more likely to experience abdominal obesity,[30] it would seem logical that they would be more likely to have increased portal vein FFA concentrations and have an increased incidence of the negative outcomes. An interesting trend emerges when collectively examining sex-specific studies of diabetes prevalence. Early investigations noted that in the United States, the only major cause of mortality where women exhibit higher rates was diabetes mellitus.[45] Further, it was the only serious chronic condition in which women exhibited higher morbidity than males. This is in contrast to more recent investigations that showed that more women have diabetes than men, but men have a greater prevalence of diabetes than women.[46] This dynamic occurs because diabetes becomes more prevalent with age, and women live to older ages than men, thereby leading to a greater amount of elderly females with diabetes. It seems that although the absolute number of women with diabetes is greater, relatively, men experience diabetes to a greater degree.

In addition to the storage of adipose tissue, females tend to preferentially metabolize fats during physical stresses, such as exercise.[47] Although this would allow women to spare carbohydrates during exercise, leading to an advantage in long-duration exercise, the ability to metabolize fats preferentially also appears important to cellular survival. Recently, it was shown that when male and female neurons are subjected to starvation, male neurons experience significantly greater autophagy (ie, controlled digestion of cytoplasmic material) and death, whereas female neurons switch to a greater use of fats and survive.[48] In humans, the relationship between the ability of female tissues to switch to a greater proportion of fat use during metabolism and prolonged life is a novel area of investigation for future research.

SEX DIFFERENCES IN LIPOPROTEIN METABOLISM

A sexual dimorphism in body fat distribution is complemented by a sex difference in systemic lipid transport and storage. For example, blood HDL concentrations are maintained in females after puberty, but decrease in males, whereas LDL concentrations are lower in females across the life span with HDLs being larger in size.[25] Moreover, LDL concentrations have been shown to decrease abruptly, whereas HDL concentrations increase progressively, with increased HDL apolipoprotein A-I and A-II levels, in estrogen-supplemented menopausal women.[49]

In contrast, supplementation with androgens in postmenopausal women has been shown to have the opposite effect: LDL concentrations increase, whereas HDL and HDL apolipoprotein A-I and A-II concentrations decrease.[50] Likewise, androgen supplementation in healthy men may initially decrease HDL-C and continue depression for the duration of testosterone supplementation.[51] Similar results were found with androgen supplementa-

tion in older men with low to normal endogenous testosterone levels.[52] Although supplementation studies may not directly mimic in vivo effects, the results of these investigations provide interesting implications about the opposing effects of sex hormones on lipoprotein metabolism. Even though a recent genome-wide association report removed some of the associations behind increased HDL and reduced cardiovascular disease risk,[53] epidemiological associations of this characteristic with improved health and reduced mortality risk cannot be ignored.

SEXUALLY DIMORPHIC MECHANISMS OF COMBATTING OXIDATIVE STRESS

The free radical theory of aging states that free radicals produced during cellular respiration cause cumulative oxidative damage resulting in aging and death.[54] Estrogens may provide antioxidant benefits due to their phenolic structure,[55,56] but also because of a role in antioxidant gene expression. This theory seems plausible because mitochondria from female rats exhibit higher antioxidant gene expression and lower oxidative damage than those from males.[57,58] Further, removal of the ovaries leads to increased mitochondrial oxidant production, whereas estrogen replacement abolishes this increase.[57,58]

Additional evidence of the role of oxidative stress in aging and a possible dimorphism between sexes comes from the measurement of 16s mitochondrial rRNA. 16s rRNA has been shown to decrease with age[59] and in the presence of oxidative stress.[60] An investigation of sex differences in mitochondrial rRNA expression in rats indicates significantly higher expression in females (700% higher than age-matched males), providing support for the hypothesis that female mitochondria function like that of younger males.[57] Continued research to determine whether these findings hold true in humans may reveal a key sex difference that contributes to differences in longevity.

In addition to estrogen, female rats have been shown to exhibit higher basal levels of the cellular antioxidants manganese superoxide dismutase (MnSOD) and glutathione peroxidase in an estrogen-dependent manner.[61,62] As a result, female tissues are better protected against oxidative damage. The combination of the antioxidant properties of estrogen and associated up-regulated antioxidant genes in females could lead to more favorable handling of the cumulative oxidative attacks that occur over the life span. For example, aging is associated with chronic states of molecular inflammation and concomitant oxidative damage to cellular integrity. Because skeletal muscle is high in mitochondrial density and oxygen flux, it is potentially exposed to higher amounts of oxidative stress. Males generally possess a greater proportion of fat free mass (notably skeletal muscle), exhibit a higher resting metabolic rate independent of body composition and fitness,[63] and therefore potentially have a greater metabolic flux of oxygen and electrons across the life span. The aging-related loss of muscle mass (termed sarcopenia) is a major occurrence in the elderly and may have oxidative injury– related causes. In elderly humans, women exhibit less sarcopenia than older men.[64] Although sarcopenia is not directly lethal, it is highly correlated with disability and mortality, and it has been proposed that this observable phenomenon be used as a biomarker of aging.[65]

SEX DIFFERENCES IN IMMUNE FUNCTION

A functioning immune system is paramount to adequate health and quality of life. Sex hormones play an important role in the sexually dimorphic nature of human immunocompetence. In general, estrogens are considered humoral immunity enhancers, whereas androgens and progesterone are considered natural immunosuppressants.[66] In fact, laboratory studies of mice have shown that males are more susceptible to infection than females, and this is attributed to differences in endogenous sex hormones.[67,68] Estrogen functions to modulate immunity via stimulating the production of anti-inflammatory cytokines[69] and inhibiting the production of proinflammatory cytokines.[70,71] However, a recent investigation in humans found that women may be at higher risk for M2 macrophage–mediated autoimmune disorders due to the ability of estrogen to increase T-helper type 2 responses.[39] The female advantage in infection resistance may serve as a disadvantage when an immune response is initiated against host cells. As such, males may be more

susceptible to infection, but females are more susceptible to autoimmune diseases. Although there are negative implications for both sexes, this tradeoff may still favor women. Mortality rates due to cardiovascular disease and cancer are orders of magnitude higher than the best indication of rates of autoimmune disease mortality in women,[72] and infectious disease, but not autoimmune disease, is a leading cause of death globally,[73] even though there is poor identification of autoimmunity-related deaths.

There is also support for the hypothesis that lower androgen levels lead to a more robust immune system.[74,75] Compared with immune responses across 3 strains of gonadectomized male mice and normal male mice injected with various antigens, female mice exhibited a greater immune response, but gonadectomy significantly increased the immune response of male mice.[74] More recently, male gonadectomy caused a more female-like immune response to bleomycin-induced pulmonary fibrosis compared with control mice, whereas androgen supplementation in female mice yielded a more male-like response.[75] These findings provide support for the possibility that decreased androgens may have a more beneficial immunological effect than increased estrogens.

HORMONAL AND CELLULAR MANAGEMENT OF STRESS

Stress, although an integral part of life, can have negative effects on the health and well-being of an individual. For example, an athlete uses progressive stresses on the body (eg, longer running duration, increased resistance training loads) to elicit physiological adaptations that will lead to greater performance (eg, higher oxygen consumption, increased strength). When the body experiences long-term exposure to a stressor or can no longer successfully defend against or adapt to physiological or psychological stressors, disease risk is increased. At the outset, it would appear that women experience greater amounts of stress and suffer to a larger degree from it. Women subjectively self-report more stress than men in response to a social stress task[76] and exhibit a higher incidence of stress-related depression.[77] However, physiological studies of the hypothalamic-pituitary-adrenal (HPA) axis stress response to psychosocial stress tests provide contrasting data.[78,79]

A collection of investigations examined the free cortisol response to anticipation of an upcoming psychological stressor, speaking and mental arithmetic in front of an audience, and bicycle ergometer exercise to exhaustion.[78] Although the exercise protocol showed similar changes in the mean cortisol level between sexes, the psychological stressor of speaking and mental arithmetic in front of an audience produced a markedly greater mean cortisol level response in males. In fact, the mere prospect of an upcoming psychological stress task produced a cortisol response in men, but not in women.[78] These findings provide insight into a sexual dimorphism of the HPA axis stress response, but because the subjects were of adult age, the data may be subject to the sociological influence of sex-based roles throughout the life span. Recent evidence suggests that differences in cortisol stress response may be abolished with age,[80] which may coincide with a narrowing of differences in endogenous sex hormones. Support for a physiological mechanism underlying the apparent difference in HPA axis stress response has been provided by a study of young children. An examination of the cortisol response to corticotropin-releasing hormone ingestion in male and female children 7 to 13 years of age found that males exhibited a significantly higher cortisol response.[79]

At the organ and cellular levels, several notable differences in the ability of female cells to deal with cellular perturbations have been documented. For example, female rodent hearts exhibit significantly less infarcted area and dysfunction than males after ischemia-reperfusion insult.[61,81] Because cardiovascular disease is 1 of the top 2 killers of both men and women worldwide, this observation is notable. This observation has been attributed to increased basal levels of cellular antioxidants (MnSOD, noted previously), as well as heat shock or stress proteins (HSPs). With respect to the latter, HSPs, in particular the 70-kDa HSP (Hsp70), represent some of the most highly conserved and cytoprotective proteins studied to date. The expression of Hsp70 is increased in several tissues in response to a wide variety of stresses and subsequently protects those tissues from future

insults. The major circulating estrogen, 17β-estradiol, appears to inhibit the stress-induced increase in Hsp70.[82,83] However, 17β-estradiol itself has been shown to elevate cardiac and skeletal muscle levels of Hsp70, a result that may account for a higher basal level of this protein in females.[84,85] HSPs can be transported (through either coordinated secretion or passive release) into the circulation and play important roles in inflammation and immunoregulation. However, the function of these extracellular proteins remains less clear. For example, in healthy adults, women exhibit twice the concentrations of circulating Hsp70 as men,[86] but centenarians and their offspring exhibit very low levels of circulating Hsp70.[87] In fact, the human Hsp70 gene is an aging biomarker candidate. In human females, genetic polymorphisms in different Hsp70 genes appear to favor longer life. More research needs to be completed to determine the significance of these findings, but, collectively, they point to a sexual dimorphism in the hormonal and cellular response to stress, which could affect at least part of the female life expectancy advantage.

WOMEN LIVE LONGER AND BETTER

Increased female longevity in the face of the adversities described here may serve as an indicator of more favorable innate biological health compared with males. If the longer life expectancy of females is accompanied by an equal or greater quality of life in aging compared with men, then this would be even more favorable. Although it was previously reported that females exhibit greater morbidity than males,[88,89] these investigations must be interpreted with caution. It has been shown that increased morbidity among females is only consistently observed using psychological measures of distress, whereas this relationship is less apparent, and sometimes reversed, in physical symptoms and conditions.[90] Moreover, after controlling for marital status, age, living arrangements, psychiatric symptoms, and role obligations, sex differences in health across many demographics are shifted to a sex-neutral or female advantage.[90–92] As such, when all factors are considered, it appears that human females have an advantage over males in not only life expectancy, but physiological health–related quality of life.

CONCLUSION

The human species have experienced an almost constant increase in life span along with ever-improving qualities of life. Advances in health care and technology have assisted in treatments of illness and disease that would have previously been debilitating or fatal while improving quality of life for those with chronic and/or terminal disease. Although this trend holds true for both sexes, there is an apparent sexual dimorphism in both life expectancy that has existed as long as records have been kept.[6] Recently, it was predicted that male children born in parts of the United Kingdom in the year 2000 would match in life span or even outlive their female counterparts once they reached 30 years of age.[8] This is an interesting prediction because there are several biological mechanisms that would suggest the sex gap in life expectancy will continue as long as the sexes exist. Even if biological mechanisms are estimated to make up only a small portion of the cause of the life expectancy gap, we believe that it is safe to theorize that although males may approach female life expectancy, parity is unattainable currently and in the near future. The complexity of the human life experience makes an examination of the primary contributors to life expectancy difficult. Nonetheless, an examination of the sex differences in not only human life expectancy, but human health in aging will prove beneficial to both sexes.

ACKNOWLEDGMENTS

Mr. Seifarth was responsible for drafting the article and revisions. Dr. McGowan was responsible for editing the article draft and final approval of the manuscript. Dr. Milne was responsible for drafting, editing, revisions, and final approval of the manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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