Chapter 9
Women's Health in the Post-menopausal Age

Donna J. Holmes

Abstract In recent human history, the trajectory of the human life cycle in industrialized cultures has undergone a profound shift. Dramatic increases (30–40 years or more) in average and maximum life expectancies have occurred, along with decreases in infant and maternal mortality rates, delays in childbearing, and fertility rate declines, plus lower mortality rates for older adults. Both the proportion and absolute numbers of older adults are growing globally, attributable in large part to the vast numbers of people born during the post-World War II "baby boom." The extension of the human life span to "extreme" old ages (80–100 years or more) has been caused by changes in culture that have outpaced biological evolution, including better nutrition, sanitation, and medical care, as well as protection against deaths from accident and exposure. An equally dramatic epidemiologic transition has accompanied this demographic change, shifting major causes of death away from infection, injury, and exposure to later-onset diseases often characterized by an extended period of disability. Women are longer-lived on average than men, and the modern "longevity bonus" means that millions of us will live a third or more of our lives in a healthy post-menopausal state. On the other hand, more older women spend their later years struggling with chronic, disabling conditions, some of which are associated with declines in estrogen and progesterone after menopause. An evolutionary analysis of these trends provides a valuable perspective on how the health consequences of an extended post-reproductive life span for modern women.

9.1 Introduction

Since the mid-1800s, a profound demographic shift has been underway for modern humans (Table 9.1). While this shift is occurring primarily in industrialized countries, the economic and health impacts associated with it are manifesting themselves globally (Olshansky et al. 1990; Olshansky 1992; Crews 2003; Vaupel 2010). Mortality rates have slowed at all stages of the life cycle, and life expectancies (defined as the probability of living to a certain age based on statistical averages for

D.J. Holmes (✉)
Department of Biological Sciences and WWAMI Medical Education Program, University of Idaho, MS 3051, Moscow, ID 83844-3051, USA
e-mail: djholmes@wsu.edu

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Table 9.1 Recent demographic shifts associated with the emergence of extremely long modern human life spans

The demographic shift since the Industrial Revolution. Since the mid-1800s, human populations in industrialized countries all over the world have experienced a dramatic demographic shift, including the following:
• Longer average life spans for both men and women
Example: Average life spans[a] in the USA:
1900: 45 years
2000s: 78–80+ years
Note: "Life span" denotes statistical average life expectancy (LE) from birth calculated for the US population as a whole. Some people lived longer than this average; others did not attain the average LE.
• Longer maximum life spans, and an increasing number of "centenarians" (people living to 100 years or more) worldwide
Longest-lived person on record, Jeanne Calment (a French woman), lived to 122 years (died in 1997)
Note: "Maximum life span" denotes the extreme case—the longest life span ever lived by anyone in a particular population for which reliable documentation of longevity is available.
• Longer segments of life spent in less-fertile or post-reproductive states
Average age at menopause: about 50 years
Average life span for women (LE at birth, USA): 80+ years
Years in a post-reproductive state: up to 30+ years
• Decreases in annual death rates at all ages
• Decreasing fertility rates
• Changes in most prevalent diseases and other causes of death to more chronic, aging-related diseases (epidemiologic shift)
• Changes in force of natural selection

Sources: Crews (2003), Finch and Austad (2008), Vaupel (2010) and National Center for Health Statistics (2012)

a particular population) at all ages have steadily increased (Table 9.2; Fig. 9.1). At the same time, fertility rates have dropped markedly. Increases in longevity have been accompanied by a dramatic "epidemiological transition": a shift in major causes of death away from the infectious diseases, famine, exposure, and accidents that plagued our ancestors, and toward a much higher prevalence of chronic diseases and disabilities associated with older ages. These unprecedented changes in rates of death and disease are manifestations of the impact of modern culture on human health, effects which have outpaced rates of evolutionary, and genetic change affecting the human physiological phenotype.

For modern women and men, a much longer segment of the life span that ever before is spent in a reduced-fertility or post-reproductive state. Millions of women can now expect to live 30 years or more (sometimes over a third of their lives) beyond menopause (around age 50), when menstrual cycles stop and circulating levels of estrogen and progesterone drop to a vestige of their levels during the fertile segment of life. This post-menopausal longevity bonus is undoubtedly one of the blessings of modern life. The health dividends of post-menopausal life, however,

Table 9.2 Shift in average life expectancy[a] for men and women combined in the USA since 1900

Year	Life expectancy at birth (years)	Life expectancy at age 65 (years)
1900	47.7	11.7
1935	60.9	12.7
2000	76.7	17.4

[a]Life expectancy is defined as the expected number of years of life remaining for a person of a given age, based on the statistical average life span for a particular population or country. Because it is calculated as an average, it represents the probability of living to a certain age; some people will outlive the average, while others will not attain it

Sources: Manton et al. (2006), Austad (2011), Bell and Miller (2005) and Holmes and Cohen (2014); Human Mortality Database (www.mortality.org)

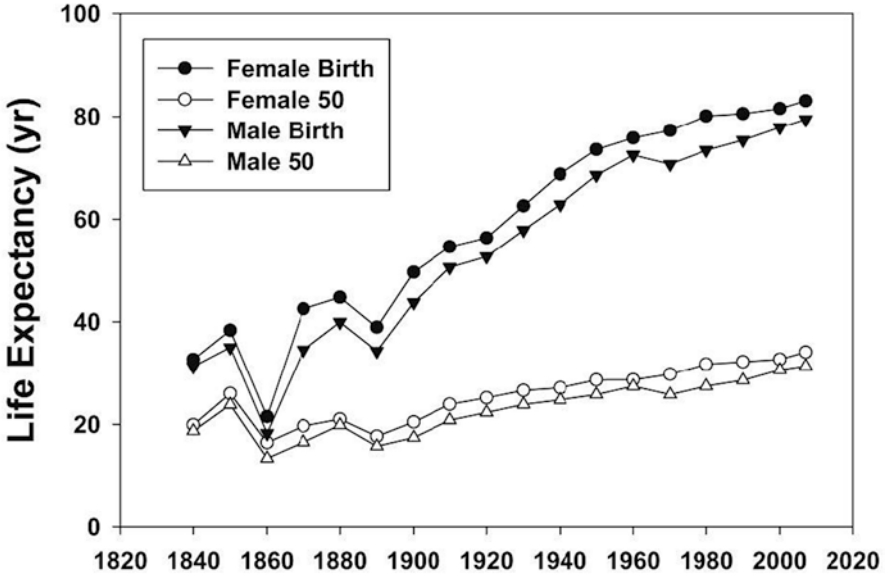

Fig. 9.1 Increases in life expectancy at birth and age 50 in females and males in Iceland. Reprinted from Austad (2011) with permission. The dip in life expectancies in Europe in the mid-1800s has been attributed to famine due to crop failure and loss of livestock, as well as epidemics of infectious diseases like smallpox, scarlet fever, and diphtheria, following the "Little Ice Age." (Appleby 1980; Guttormsson and Garðarsdóttir 2002)

come packaged with some subtle—and often unrecognized—physiological trade-offs. In many ways, postmillennial women are exploring new physiological territory as we reach old age in unprecedented numbers, and face the challenges of sustaining optimal health during the decades after menopause. The aim of this chapter is to couch these physiological trade-offs and health challenges in evolutionary terms and in the context of our ancestral physiological heritage. We also consider some of the implications of the recent shift in women's life expectancy as viewed through the lens of evolutionary medicine.

9.1.1 Biogerontology

Many of the health challenges experienced by women in the modern world at midlife and beyond can be analyzed using a conceptual framework from the evolutionary biology of aging, also referred to as "*biogerontology*" (Rose 1991) or "geroscience" (Lithgow 2013; Kennedy et al. 2014) (Table 9.3). Biogerontologists integrate methods from a variety of disciplines—evolutionary theory, demography, genetics, comparative physiology, and developmental biology—to understand the biology of human aging in the context of evolution and natural history, as well as in a broader comparative framework. The field of biogerontology incorporates *evolutionary aging theory*, a set of ideas that can be applied to understand the phenomenon of aging in terms of Darwinian evolutionary theory. Aging theory has gradually matured since the 1950s, in close association with evolutionary life-history theory (reviewed in Kirkwood and Austad 2000; Finch and Austad 2008; Cohen and Holmes 2014) (see references cited in Table 9.3).

A central idea from biogerontology is the prediction that fitness trade-offs shape organismal life histories to promote lifetime reproductive success (Kirkwood 1981; Rose 1991; Stearns 1992; Partridge and Barton 1993). Since reproduction is costly, successful populations of organisms are expected to evolve strategies that sacrifice long-term maintenance and repair of somatic (non-reproductive) structures in order to maximize lifetime reproductive effort. Differences in mortality rates are seen as the major force driving natural selection. Variation in mortality rates, in turn, is predicted to shape life-history trajectories along a continuum of short-lived, fast-reproducing vs. longer-lived, slower-reproducing organisms. As the likelihood of survival and successful reproduction declines over the course of an animal's life span, the force of natural selection wanes, and the probability of aging-related deterioration, dysfunction, and disease is expected to increase.

An important tenet of evolutionary aging theory (also referred to as "*senescence theory*") is that aging (organismal "senescence") is not expected to be adaptive. Since aging cannot directly promote the reproductive fitness of the individual, evolutionary biologists generally do not view aging as the result of a "program" directly shaped by natural selection (Williams 1966). Instead, aging is expected to arise by default, as a by-product of the *failure* of evolution to promote a longer reproductive life span and extended period of organismal integrity. Another key idea from evolu-

Table 9.3 Key concepts and processes from the biology of aging ("geroscience" or "biogerontology") and evolutionary aging theory

Aging (organismal senescence) can be defined as a deterioration of physiological function with advancing chronological age, leading to an increased probability of disease, disability, and death.
General characteristics of aging:
Aging is
• Not "programmed" or shaped directly by natural selection, hence generally not expected to serve a primary adaptive function
• Correlated in its timing to the failure of developmental or physiological events critical for reproductive success earlier in life (e.g., infertility in female mammals is linked to finite stores of oocytes formed during prenatal development)
• Often has an unpredictable trajectory for individual organisms in a given population, with different systems often deteriorating at different rates
Evolutionary processes ("ultimate mechanisms") proposed to be involved in aging:
• Increasing probability of disease, deterioration, and death with chronological age
• Waning natural selection with age, as mortality force and probability of reproduction decline
• Accumulation of mutations in older individuals in a population
• Accumulation of molecular and cellular damage with age
• Gradual failure of repair mechanisms
• Fitness trade-offs between investment in reproduction vs. maintenance and defense of somatic tissues (life-history trade-offs)
• Deleterious effects later in life of genes with beneficial effects earlier in life (antagonistic pleiotropy)
Basic biological processes ("proximate mechanisms") proposed to be involved in aging:
• Oxidative stress and other forms of damage to macromolecules, cells, and tissues (including damage to DNA)
• Mitochondrial dysregulation
• Dysregulation of transcription, cell replication, and cellular signaling patterns leading to unregulated cell growth
• Failure and dysregulation of inflammatory and autoimmune processes
• Changes in lipid metabolism
• Changes in energy metabolism
• Endocrine processes involved in growth and reproduction
• Failure of mechanisms for homeostasis and repair

References: Williams (1957), Rose (1991), Partridge and Barton (1993), Finch and Kirkwood (2000), Kirkwood and Austad (2000), Zera and Harshman (2001) and Holmes and Cohen (2014)

tionary aging theory is that genes or physiological processes that are beneficial for development or reproduction early in life may exert correlated, deleterious effects later in life. This phenomenon, "*antagonistic pleiotropy*" (Williams 1957), can help to explain why some essential endocrine and cellular processes may become dysregulated and even harmful at older ages. An additional tenet of evolutionary aging theory is that harmful mutations in a population are more likely to accumulate and be expressed later in life, as the force of natural selection wanes.

To understand the complex health issues associated with living longer lives, evolutionary biologists can compare health and life span variables for humans living in modern, industrialized cultures with those of traditional hunter-gatherer societies (see, for example, Gurven et al. 2008, 2009). Another approach is to compare clinical health variables, reproductive aging, and mortality patterns in modern people with those of nonhuman primate species living in captivity or in the wild, or those of non-primate mammalian or vertebrate species with different social lives and life spans (see, for example, Cohen 2004; Finch and Holmes 2010). Yet another comparative evolutionary approach to understanding aging and health is to study variation across species in genes, cell-signaling pathways, and hormones responsible for life span, basic aging processes, or specific aging-associated diseases in nonhuman animals, and attempting to place these functions in adaptive context in healthy, reproductive animals (Tatar et al. 2003; Ackermann and Pletcher 2008; McDonald 2014).

Evolutionary approaches like these help to identify the molecular, cellular, and physiological changes associated with variation in life span, basic aging processes, and some diseases of aging in humans (for reviews, see Kirkwood and Austad 2000; Promislow et al. 2006; Finch 2007). A continued application of evolutionary principles to specific aging-related conditions—including those experienced during and after the menopausal transition—can provide a framework for understanding specific physiological and endocrine trade-offs likely to be associated with living beyond the reproductive life span for women in the new millennium.

9.2 "Extreme Aging"

Modern humans in industrialized countries generally now live approximately 35–40 years longer on average (and up to 50 years longer at the upper extremes of life span) than even our very recent ancestors. In the USA, the average life expectancy at birth (for women and men combined) has increased from about 47 (1900) to over 76 years (2000) over the past century or so (Vaupel 2010; Austad 2011) (Tables 9.1 and 9.2; Fig. 9.1). In Japan (the longest-lived country in the world) and some other developed nations, average life spans for both sexes now exceed 80 years. While the majority of this longevity increase is due to declines in infant, child, and maternal mortality over the past two centuries, life expectancies have increased significantly at older ages, as well. Americans who have reached age 65 today can expect to live another 17 years or; this is 6 years longer than the predicted life span at age 65 in 1900. Due, in part, to increases in the size of the global population as a whole, many million more people than ever before are living past the age of 100 years. Some demographers argue that the absolute upper limits of human life span have not yet been reached, and that some babies born in this decade can expect to live over 130 years (Carnes et al. 2003; Vaupel 2010).

Longer life expectancies mean that we are now routinely outliving our ancestral reproductive life span. Some of our forebears, like some people living in traditional, unindustrialized cultures today, also outlived their fertile years, and older adults in

both traditional and modern societies clearly can make substantial cultural contributions when they do survive into grandparenthood (Kaplan 1997; Hawkes et al. 1998; Hawkes 2004). But the current consensus among human demographers, biogerontologists, and evolutionary biologists is that life spans of over 50 years were achieved very rarely among ancient humans, and that before the industrial revolution most people lived less than 35 years—an age marked by waning fertility in modern humans, both male and female (Crews 2003; Finch and Crimmins 2004; Finch 2007; Olshansky 2014). The continuing shift toward lower mortality rates and higher life expectancies for modern people is persuasive evidence that, on average, modern people are indeed healthier, and tend to remain infection—and accident-free much longer than either our ancestors or modern counterparts still living in traditional cultures.

The recent cultural and technological innovations responsible for the modern demographic and epidemiological shift include improvements in medical care, public sanitation and safety, nutrition, and health education. By altering our environment, we have successfully altered the causes of human mortality and, in evolutionary terms, transcended the shadow of natural selection that hung over humans in centuries past. This new and growing likelihood of survival into an extended post-reproductive life span represents an unprecedented gift of modern life. But at the same time, a more "extreme" life spans means that many more of us face a much longer segment of life dealing with diseases associated with aging, including cardiovascular disease, cancers, chronic obstructive pulmonary disease, and dementias. We also confront a much higher prevalence of potentially disabling aging-related conditions, such as musculoskeletal problems (including osteoarthritis and osteoporosis), sensory deficits, and incontinence.

9.2.1 Ancestral Life spans in Perspective

From Paleolithic times until the 1800s, human populations generally experienced much higher mortality rates at all ages than those in industrialized cultures (Crews 2003; Finch and Crimmins 2004; Finch 2007), with *most* ancient people living less than 30 years. According to evolutionary theory, the force of natural selection is limited to the reproductive segment of the human life span. As fertility wanes, so does the force of selection. In a discussion of modern human demography in evolutionary perspective, Crews (2003) stated that "Australopithecines and early *Homo* species are estimated to have averaged only about 15–20 years of life over the 280,000 – 350,000 generations they prowled the earth…, while over 40 generations of early agriculturalists and nomadic pastoralists could expect to live only about 25 years…."

While some of our ancestors are likely to have lived beyond their peak reproductive years on average, and the *maximum* life span in some populations may exceeded this period, the average life expectancy for most prehistoric human populations was in all probability under 40 years (Table 9.2). According to evolutionary theory, aging is expected to occur outside the window of strong selection, after the probability

of reproduction has declined significantly. Hence it is not surprising that the prevalences of aging-related diseases increase sharply after age 30, and that the slopes of increasing prevalence of many diseases and forms of disability (including cardiovascular disease, cancers, osteoarthritis, and osteoporosis) rise again after age 50, when reproduction ceases for women (Figs. 9.2, 9.3, 9.4, and 9.5).

9.2.2 The Female Longevity Paradox

Human females, like females of many other mammalian species, exhibit lower mortality rates than males at all life stages (Austad 2006, 2011). Women live significantly longer than men worldwide, and older women die at lower rates at all ages from cardiovascular diseases and cancers. Despite the fact that women are better survivors on average than men, however, older women tend to have higher rates of comorbid diseases (occurring together) and disabling conditions—including dementias, blindness, obstructive lung disease, obesity, and painful, chronic musculoskeletal problems (Figs. 9.3, 9.4, and 9.5). Since more women than men remain alive at older ages, the total population of women with potentially deadly or disabling aging-related diseases far exceeds that of men in industrialized nations (World Health Organization 2003).

The extended life spans enjoyed by humans in the twenty-first century are a product of cultural innovations, rather than rapid evolutionary changes in human biology. The reproductive segment of the human life course can be seen as the product of developmental programs and physiological trade-offs evolved to optimize reproductive success in ancestral environments. In all likelihood, however, these fitness trade-offs did not arise as a direct result of natural selection to optimize our *health* in the latter third of our lives. Our bodies were not "designed to fail"; rather, some of the health challenges now associated with aging can be understood as by-products of physiological processes optimized for reproduction, rather than for sustained health under conditions of extreme longevity.

9.3 Menopause

9.3.1 Endocrine Pleiotropy

Steroid reproductive hormones, like estrogen and testosterone, provide a particularly good illustration of how specific physiological mechanisms involved in reproductive trade-offs can be implicated in aging-related conditions. Sex steroid hormones are pleiotropic: that is, each hormone has multiple phenotypic effects (Zera et al. 2007; Bribiescas and Ellison 2008). They act during critical periods of development, coordinating physiological functions with environmental or social

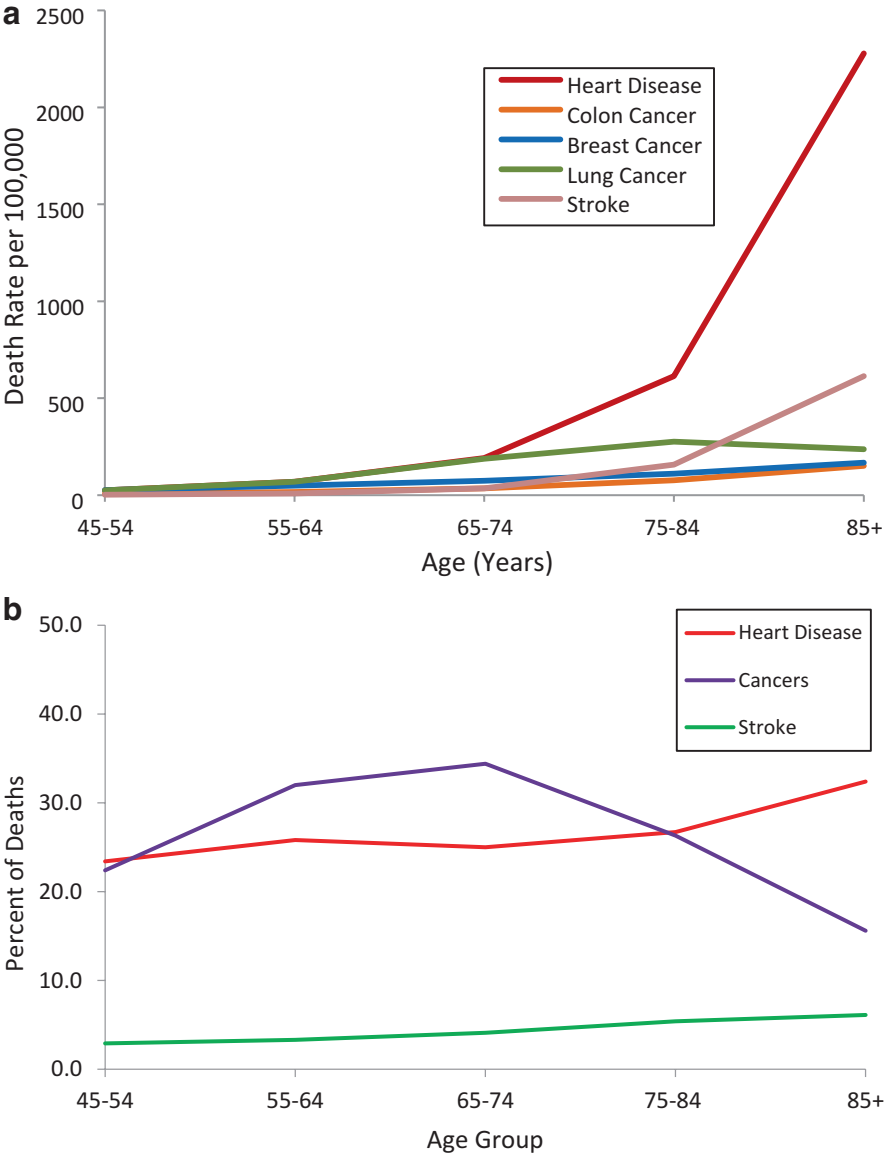

Fig. 9.2 (**a**) Death rate or (**b**) percent of deaths from several leading causes of death in older (**a**) women and (**b**) men in the USA in 2009. Mortality from heart disease and stroke for women increases at much higher rates with age than from breast, colon, or lung cancer (death rates for women expressed as crude rates per 100,000 population, all races combined). *Data source*: Centers for Disease Control and Prevention, National Center for Health Statistics, CDC WONDER Online Database, 2012

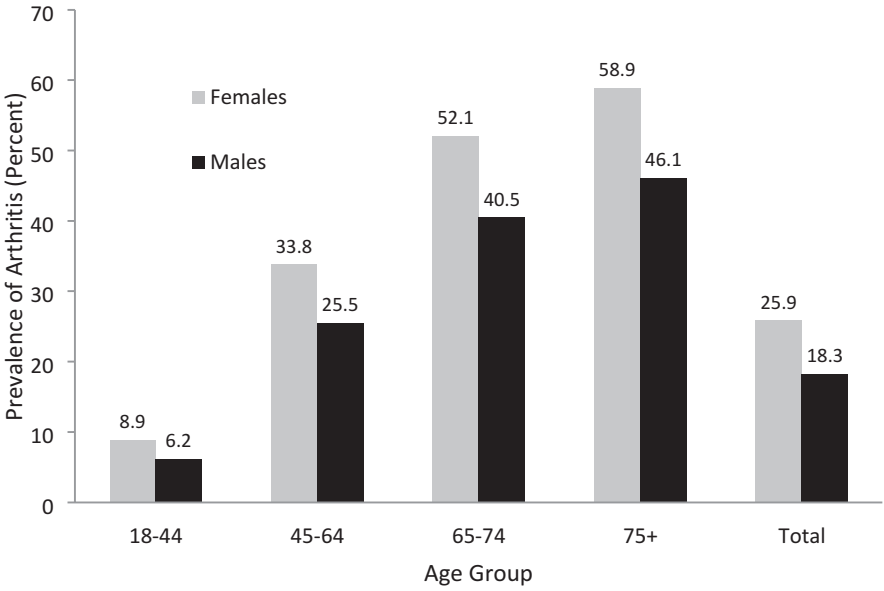

Fig. 9.3 Sex differences in prevalence of osteoporosis in adults (all races combined) at different ages in the USA, 2005–2008. Prevalence is expressed as percent of people in each group. *Data source*: National Institutes of Health (2011). Redrawn with permission

cues so as to fine-tune developmental or reproductive timing. In the context of life-history evolution, reproductive hormones are among the primary mechanisms likely to mediate fitness trade-offs shaped by natural selection. They are important for maintaining phenotypic plasticity, and provide physiological mechanisms for calibrating adaptive responses to environmental variability (Bribiescas and Ellison 2008; Gilbert and Epel 2008; Gluckman et al. 2009) (refer to introductory material on hormones, nutrition, timing of menarche, etc.). Sex hormones are associated in particular with the evolution of strategies for energy allocation and life-history trade-offs between reproduction and self-maintenance. At older ages, however, after fertility has waned, the physiological landscape of these endocrine trade-offs shifts. Hormones that were essential for reproduction—or the absence of these hormones—can have important, and sometimes paradoxical, effects on the health of older humans.

9.3.2 Human Menopause in Comparative Context

The most straightforward physiological explanation for human menopause is ovarian aging. Menopause marks the depletion of finite stores of viable oocytes, accompanied by declining levels of estrogen and progesterone followed by the cessation of ovulation and, ultimately, infertility. While humans are unusually long-lived

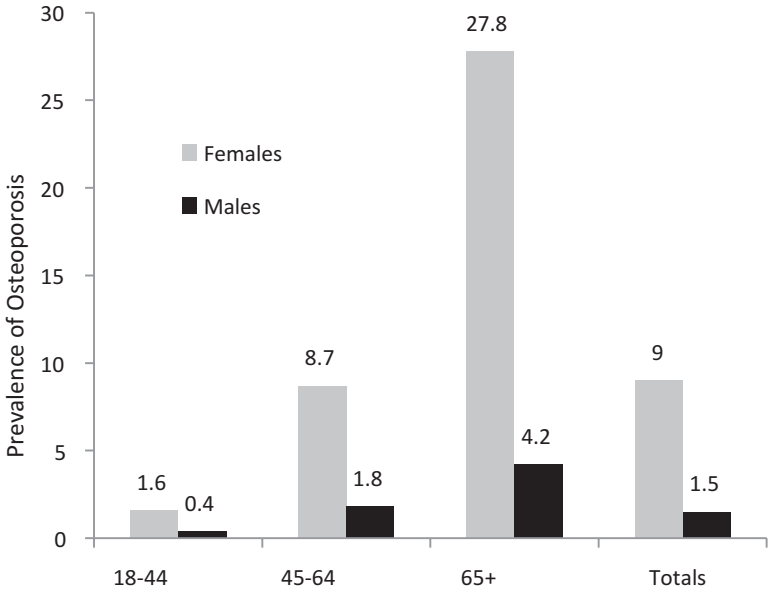

Fig. 9.4 Sex differences in prevalence of osteoarthritis in adults (all races combined) at different ages in the USA, 2007–2009. Prevalence is expressed as percent of people in each group who reported a diagnosis of osteoarthritis by a medical professional. *Data source*: National Institutes of Health (2011). Redrawn with permission

for our average body size, a life cycle marked by midlife cessation of fertility followed by a post-reproductive period of some length is not unique to humans. The underlying physiology of ovarian failure is poorly studied in many nonhuman animals (with the exception of laboratory rodents), but comparative surveys show that many other female vertebrates, including nonhuman mammals, exhibit reproductive aging patterns consistent with the depletion of ovarian reserve (for reviews, see Austad 1994; Cohen 2004; Finch and Holmes 2010). Female post-reproductive life spans of up to a third of the total life span are documented in eight separate mammalian orders, suggesting that the underlying ovarian physiology is evolutionarily conserved. These examples are not limited to species with particularly long life spans, well-developed maternal care, or extended kin networks. Post-menopausal life spans have also been documented in rodents, domestic birds (e.g., Japanese quail), and some captive wild fishes (e.g., guppies) (Holmes et al. 2003; Reznick et al. 2006; Finch and Holmes 2010). Post-reproductive life spans are more likely to be seen when animals are maintained in captivity and protected from natural sources of mortality. In nature, they appear to be much rarer, and limited to long-lived, highly social vertebrates like elephants and pilot whales.

Extended post-reproductive life spans in humans and other social mammal species with well-developed parental care and overlapping generations have been suggested to represent an adaptation for increasing females' inclusive fitness (reproductive success of close kin) and for enabling grandmothers to assist

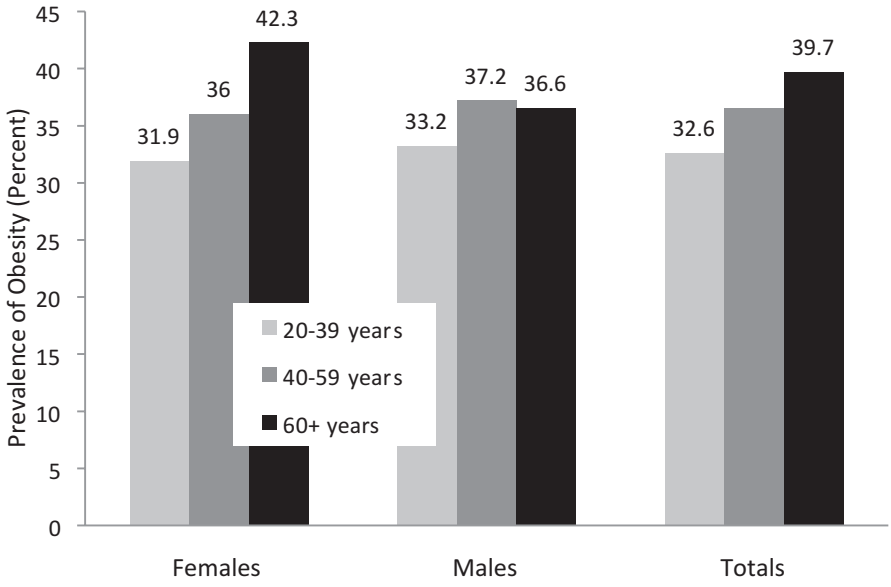

Fig. 9.5 Sex differences in prevalence of obesity in adults (all races combined) of three different age groups in the USA, 2007–2009. Prevalence is expressed as a percentage of each group. *Data source*: National Institutes of Health (2011). Redrawn with permission

with care and provisioning of grandoffspring. Healthy grandmothers (and grandfathers, as well) clearly do make social and nutritional contributions that benefit younger kin (Kaplan 1997; Hawkes et al. 1998; Hawkes 2004; reviewed in Jasienska 2013). However, *the female reproductive life span in humans, as well in other animals, likely reflects selection by ancestral mortality forces, and corresponds to the likelihood of survival in past environments.* As the likelihood of survival in modern cultures has become uncoupled from ancestral mortality risk, vast numbers of women are living much longer now than ever before in a post-reproductive state. In the face of this more extreme modern longevity, the loss of circulating sex steroids has new and significant consequences over the longer term.

Menopause is considered to be a healthy reproductive transition, rather than a pathological state (Goodman et al. 2011; Stuenkel et al. 2012). Nonetheless, many of the health issues now facing older women arguably are associated with living significantly longer than ever before in a state characterized by low—or post-reproductive levels of reproductive hormones. We need not view this newly extended segment of the life span in "either-or" terms of adaptation vs. pathology. Instead, the post-menopausal years can be seen as a "new normal"—constrained to some extent by past selection for reproductive success, but now representing a special phase of the life cycle in which longer-term health may be optimized using strategic new approaches to disease prevention and intervention, as informed by an evolutionary perspective.

9.3.3 Estrogen and Health

The concept of endocrine pleiotropy is particularly relevant to aging-related health and disease in women. Estrogens promote gamete development, as well as growth and cell proliferation in target reproductive tissues—actions that are essential for female sex differentiation and reproduction. As the ovaries regress at menopause (around age 50), estrogen and progesterone levels drop precipitously. In modern humans, the timing of menopause corresponds with changes in the slopes (rates of increase) of age-specific prevalences of many diseases—including cardiovascular disease and some cancers—as well as increased rates of mortality (Fig. 9.2).

Loss of estrogen is clearly linked to such potentially disabling, aging-related conditions as osteopenia and osteoporosis, which are characterized by depletion of calcium in bones that can result in bone fragility, frailty, falls, and fractures. Osteoporosis affects older women in far greater numbers than men (Fig. 9.3). Estrogen may, moreover, play a role in preventing osteoarthritis, another aging-related condition that disables more women than men (Fig. 9.4). Estrogen loss is also clearly responsible for troublesome symptoms many women experience during the menopausal transition and beyond (Goodman et al. 2011; Stuenkel et al. 2012). Some of these are serious enough to cause real distress and require medical intervention—including hot flashes or flushes, vulvovaginal atrophy, painful intercourse, and loss of libido. Many women experience additional symptoms that significantly impact their well-being, including anxiety, difficulty sleeping, memory problems, and irritability.

A wealth of research of various types (including clinical, epidemiological, and laboratory animal studies) suggests that, at least under certain physiological conditions, estrogen has cardioprotective, neuroprotective, anti-inflammatory, and antioxidant properties (reviewed in Brinton and Nilsen 2003; Chen et al. 2006; Moolman 2006; L'Hermite et al. 2008; Bay-Jensen et al. 2012). Estrogen loss is linked by several lines of evidence to cardiovascular disease, including heart attack and stroke. The precise nature of this link remains controversial and is currently an intense focus of research. Epidemiological studies of the effects of early (surgical or natural) menopause suggest that estrogen protects against cardiovascular disease, and decreases the overall mortality rate in older women (see, for example, Mikkola and Clarkson 2002; Rocca et al. 2006; Stuenkel 2012). One recent study of over 2500 women aged 45–84 presented evidence that a subset of about 693 woman reporting menopause (surgical or natural) at the age of 46 or younger had approximately double the risk of heart disease or stroke compared to women reaching menopause later (Wellons et al. 2012).

The "dark side" of estrogen pleiotropy involves its capacity to promote the proliferation of cells (including cancer cells) in target tissues. Estrogen is clearly implicated as a risk factor for various reproductive cancers (breast, uterine, and ovarian) in women, and prevalence rates of all reproductive cancers increase with age (American Cancer Society 2013) (Fig. 9.2a). (Although men can get breast cancer, and it can be deadly in men, it is predominantly a women's disease.) Interestingly,

however, rates of cardiovascular disease and dementia increase much more dramatically for women after menopause, suggesting a protective role for estrogen. Current research suggests that there is a "window of opportunity" for the therapeutic effects of estrogen therapy, however, with past exposure to endogenous levels of this hormone being a key predictor of therapeutic action, as well as the risks of cardiovascular disease and reproductive cancers later in life. This therapeutic window is reminiscent of the critical periods for hormone action associated with milestones during normal development and the reproductive life span.

Some very large and well-publicized controlled clinical trials, including the Women's Health Initiative (WHI) study in the USA, have shown an increased risk of breast cancer and stroke in women who started hormone therapy (estrogen combined with progestogen) late (in the late 1950s or older, well after the menopausal transition), and continued it for an extended period of time (Roussouw et al. 2007; Harman et al. 2011). In the WHI study, however, as well as some later clinical trials, hormone therapy has been shown to pose very little health risk for younger menopausal women (starting around age 50) when used to treat troublesome symptoms for five or more years during and after the transition. These findings reinforce the idea that a single hormone may have pleiotropic effects—some good and some bad—and that during reproductive aging, as during earlier development, the timing of hormone action is critical. Researchers attempting to develop strategies for safe treatment of menopausal symptoms are currently conceptualizing an optimal "window of opportunity" during the reproductive aging process intended to balance benefits and risks of hormone therapy. While estrogen currently is not approved for the prevention of aging-related diseases except osteoporosis (i.e., low-dose transdermal patch), the physiological complexity of the role that this hormone plays in cardiovascular and neurological disease, including dementia, is still a focus of intense study and debate. A number of prominent clinician–researchers have argued for a greater role of estrogen therapy in the primary prevention of aging-related disease (Langer et al. 2012; L'Hermite 2013).

The arc of life has shifted dramatically for modern humans. As the baby boomers approach old age, we are participating in a demographic and epidemiological revolution. The extension of longevity far beyond the fertile life span, while not a common part of our ancestors' life history, has become the "new natural."

We are living longer, largely healthier lives in industrialized countries because we have been released from the selection pressure and sources of mortality that our ancestors experienced. Viewed in this evolutionary context, and in terms of the relative recency of historical changes in the human life span, it is not surprising that we face new challenges for optimizing health during the latter third of life. Millions of us are living outside the "selection shadow" (Kirkwood and Austad 2000) that shaped our ancestral life span, and we are now faced with "new" (in terms of increased incidence in the population) set of chronic diseases and disabilities associated with modern life.

The benefits and blessings of living longer, healthier lives are obvious. The "down side" of living to older ages is that we are now surviving long enough to contract diseases of aging that seldom affected humans in past eras, including

cancers, diabetes, dementias, cardiovascular disease, and chronic obstructive pulmonary disease. In addition, we are encountering in the modern environment new physiological challenges, with which we may be rather poorly designed to cope for the long haul (Finch and Crimmins 2004; Finch 2007; Gurven et al. 2008). These include extended periods of exposure to physiological stressors, toxins, and potentially damaging metabolic by-products, including inflammatory compounds and products of oxidative metabolism implicated in aging and disease (reviewed in Holmes and Cohen 2014). The negative effects of modern overnutrition and a sedentary lifestyle, moreover, may combine with those of an extended post-reproductive life span, in which levels of sex hormones are very low, producing higher rates of potentially disabling conditions in older women like osteoporosis, osteoarthritis, diabetes, and obesity.

9.3.4 Surviving into the Gray Zone

Living in this evolutionary "gray zone" of extreme longevity poses some new (and sometimes paradoxical) health challenges. Menopause, with its associated changes in levels of estrogen and progesterone, presents a case in point that is challenging in its physiological and cultural complexity. Extended post-menopausal life spans may not have been a "natural" feature of our ancestors' life histories, but they are now normal for millions of women in industrialized countries (see, for example, Pollycove et al. 2011). Many otherwise healthy women experience—and request medical support for—challenging symptoms during and following the menopausal transition. Although these symptoms vary a great deal among modern cultures, in the USA and Europe they are problematic for many women. In the USA and Europe, clinical trials and reliable survey data show that over 20 % of women experience menopausal symptoms troublesome enough to significantly affect their overall well-being, including vasomotor symptoms (hot flashes or flushes), cognitive issues, anxiety, irritability, and changes in sexual functioning (Sowers et al. 2013; L'Hermite 2014). Up to 40 % of women, moreover, experience less severe symptoms. As the cultural context for menopause has shifted along with the life course, expectations for health and well-being for older women have changed as well.

9.3.5 Windows of Opportunity

The health effects of steroid hormones during aging, as during reproductive life, are dependent on life stage and physiological context. Their effects on older women are also pleiotropic, with multiple, complex impacts on health, disease risk, and longevity. Like many other aspects of aging, the effects of sex steroids are unpredictable, individually variable, and difficult to place into an adaptive context, in which physiological phenomena are expected to have a phenotypically adaptive range of effects.

As the life spans of modern women have lengthened, weighing the medical trade-offs associated with estrogen therapy during the menopausal transition and beyond has become a major challenge for medical practitioners and the research community concerned with older women's health.

Post-menopausal women are at increasingly greater risk of breast cancer as they age, and this risk can be increased by the use of menopausal hormone therapy. The risks of death and disability from heart disease and stroke, however, are much higher, and increase with age at a much higher rate in older women (Fig. 9.2a). Estrogen may afford protection against cardiovascular disease. Current thinking in the clinical menopause research community is that there are critical windows of time for treating menopausal symptoms that can afford an acceptable balance between benefits and risks. The concept of *critical clinical windows* echoes that of critical periods of responsiveness to endogenous hormones during development. During reproductive aging, however, these windows are dissociated from their earlier developmental and reproductive contexts, in which the maximization of adaptive reproductive trade-offs is paramount—sometimes at the expense of long-term health and survival.

Women living into the age of grandmothering undoubtedly make social, economic, and other contributions to their extended social networks, regardless of the culture in which they find themselves. On the other hand, most modern women are delaying or significantly reducing their reproductive output, or have foregone reproduction altogether. Ideally, health priorities in the new millennium take into account these changes in the arc of women's lives, and focus on maximizing healthy life span and physical, social, and psychological well-being for women, while recognizing that we are not entirely free of ancestral physiological and evolutionary constraints.

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